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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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CONTENTS

Original Communications

Interruption of the Sympathetic Nervous System in Relation to Trauma. Lieutenant Colonel M. Dawson Tyson and Captain John S. Gaynor, Medical Corps, Army of the United States ---- 167

Abdominal Apoplexy Secondary to Ruptured "Congenital" Aneurysm. Thomas A. Shallow, M.D., Peter A. Herbut, M.D., and Frederick B. Wagner, Jr., M.D., Philadelphia, Pa. ---- 177

Penicillin Therapy of Infections in 220 Patients. Major Joseph E. Hamilton, Major Andrew G. Prandoni, Major Jack M. Evans, and Captain Monroe J. Romansky, Medical Corps, Army of the United States ---- 186

A Safety Factor in Gastric Resection. L. A. Alesen, M.D., Los Angeles, Calif. ---- 220

Hyperuricemia in Gastric Cancer. Bernard J. Ficarra, M.D., Brooklyn, N. Y. ---- 223

Multiple Carcinomas of the Stomach. Julian A. Rickles, M.D., Miami, Fla. ---- 229

Early Diagnosis and Management of Small Intestinal Obstruction. Claude J. Hunt, M.D., Kansas City, Mo. ---- 237

Fissures of the Articular Cartilage of the Patella. Major Charles J. Sutro, Medical Corps, Army of the United States ---- 251

Inguinal Hernias and Allied Defects in Naval Recruits. Lieutenant Commander Charles W. McLaughlin, Jr., and Lieutenant Commander John Reid Brown, Medical Corps, U.S.N.R. ---- 267

Editorial

The Use of Chemotherapy in the Secondary Closure of War Wounds of Soft Parts. Champ Lyons, M.D., New Orleans, La. ---- 275

Recent Advances in Surgery

Sympathectomy and the Circulation—Anatomic and Physiologic Considerations and Early and Late Limitations. Keith S. Grimson, M.D., Durham, N. C. ---- 277

Book Reviews

Book Review ---- 299

Books Received ---- 299

Announcement

Urology Award ---- 302

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SURGERY

VOL. 19 FEBRUARY, 1946 NO. 2

Original Communications

INTERRUPTION OF THE SYMPATHETIC NERVOUS SYSTEM IN RELATION TO TRAUMA

LIEUTENANT COLONEL M. DAWSON TYSON AND CAPTAIN JOHN S. GAYNOR, MEDICAL CORPS, ARMY OF THE UNITED STATES

TOTAL war has created a necessity heretofore unequaled of observing the effects of trauma applied to the human body in every conceivable form. As predicted by Livingston[1] and later pointed out by de Takats,[2] the opportunity, largely absent between wars, for studying any considerable number of cases of post-traumatic painful and vasospastic states has been revived.

Interruption of the sympathetic nervous system applies chiefly in three general categories, all of which are probably related to improvement of the circulation at the site of trauma. These groups are as follows:

(1) Post-traumatic painful and vasospastic states with or without Sudeck's osteoporosis. This group includes those cases where reconstructive surgery is contemplated in the presence of a dangerously reduced circulation.

(2) Injury of the main arterial supply of an extremity.

(3) Acute trauma, particularly fractures and crushing injuries of the hands and feet.

Out of the mass of material which is accumulating it is hoped that sufficient information may be obtained to clarify many of the perplexing problems which now confront the profession in dealing with these cases, thereby reducing discomfort, malfunction, and prolonged hospitalization in many individuals.

In this Army General Hospital in the Zone of the Interior, wounded have been received from all theaters of war and from surrounding station complements. It has been illuminating to observe the large number of individuals who have sustained mild or severe trauma of the extremities who are suffering, in addition, from vascular abnormalities and minor causalgia (Homans[3]) related to the trauma. These minor causalgias and vasospastic states complicating trauma result in considerable malfunction and delay in convalescence. When pain is severe, though not even reaching the degree of a true causalgia (Mitchell[4]), varying degrees of deterioration of the personality may, in time, result.

Received for publication, July 31, 1945.

As examples of vasospastic and causalgic states complicating trauma, the following illustrative cases are cited.

CASE REPORTS

CASE 1.—A 28-year-old private had a past history indicating a rather unstable emotional make-up, and his adjustment to Army life had not been very satisfactory. In September, 1944, this soldier experienced a sudden sharp pain in the right middle finger. There was no previous injury or known inciting cause. A diagnosis of tenosynovitis was made and a lateral incision on one side of the finger was carried out. It is stated that a drop or two of pus was obtained, but the history is not too clear on this point. The incision healed quickly leaving a nonadherent scar. Concomitant with this episode the hand became cold and sweated profusely. Its color varied from bright pink in a warm environment to livid on exposure to cool air. Pain was a predominant feature, and prohibited any use of the hand. Physical therapy increased the pain. Pressure on any part of the hand was borne with difficulty and there was a continual dull ache which seemed to be situated deep in the palm and occasionally shot to the elbow. The patient's sleep was interfered with and he became increasingly nervous and apprehensive. He was admitted to this hospital Nov. 9, 1944, at which time it was noted, in addition to the findings mentioned, that the tissues of the right hand were swollen, the normal creasess were shallow or obliterated, and the skin was atrophic and shiny. The color changes were striking, as previously noted (Fig. 1). The patient stated that all the fingers felt stiff. Limitation of flexion of the fingers was present. X-rays of the right hand (Fig. 4) showed a moth-eaten osteoporosis (Sudeck's). The patient's appearance suggested the possibility of hyperthyroidism, but investigation along this line produced negative results.

Nov. 13, 1944, a novocain block of the right stellate ganglion was done. The hand became warm and pink and remained so for four hours. During this time the pain was decreased, but returned with all its previous intensity. The improvement with blocking definitely implicated the sympathetic nervous system. Since the amelioration of symptoms was of short duration, and in view of the patient's mental state, a permanent interruption of the appropriate sympathetic fibers was decided upon in preference to a continuation of novocain blocks. Sympathectomy was done on Nov. 20, 1944. The hand became warm and dry and there was a change in the consistency of the soft tissues in twenty-four hours. Edema disappeared, the normal creases became deeper, and motion of the fingers was less restricted (Fig. 3). There was a steady diminution of pain so that in about two weeks normal pressure of the hand caused no discomfort and the subjective discomfort was much improved. There was no further radiation of the pain to the elbow. X-ray of the hand about four weeks postoperatively (Fig. 4) showed an almost normal bony structure. Unfortunately, the patient's psychoneurotic manifestations showed only slight improvement and he was discharged on a Certificate of Disability.

CASE 2.—A 22-year-old private mangled his left thumb in a wood router three years before admission to this hospital on Nov. 21, 1944. The injury resulted in extensive scarring of the soft tissues of the thumb with deformity and limitation of motion of this digit. The hand became cold and moist and presented the color changes described in Case 1, although more severe (Figs. 5 and 6). Pain was an outstanding feature in this case. The hand was kept continually in the pocket to keep it warm and away from trauma. The slightest touch on the thumb was unendurable and because of this, use of the hand was prohibited. None of the modalities of physical therapy could be tolerated. On several occasions, novocain blocks of the thumb had been done to permit trimming of the nail. X-rays showed typical Sudeck's osteoporosis. Infiltration of the tight scar on the thumb with 2 per cent novocain enabled the thumb to be moved without pain, but deep pressure was still painful and there was no release of vasospasm of the hand. Three successful novocain blocks of the left stellate ganglion produced the characteristic changes in the hand and cessation of pain, but the effects lasted only about one-half hour. Undoubtedly a sympathectomy should be performed on this patient, following which the desirability of plastic and orthopedic procedures

SURGERY
VOL. 19, NO. 2, FEBRUARY, 1946

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Appearance of hands two weeks prior to operation, showing edema of dorsum, right hand, and fingers; the shiny atrophic condition of skin of fingers is apparent.

Fig. 2.—The mottled cyanotic appearance of the right hand is well shown.

Fig. 3.—Condition of right hand one week after right dorsal sympathectomy; the skin is wrinkled and less shiny, and there is no color difference in the two hands.

on the thumb can be evaluated. His surgical program is still under consideration. It is noteworthy that this patient does not show marked personality changes except for a rather natural tendency to remain withdrawn from others and to play a spectator's role both at work and recreation.

CASE 3.—A private was admitted to this hospital on Sept. 28, 1943. July 26, 1943, he had sustained compound comminuted fractures of the left tibia and fibula and paralysis of the common peroneal nerve. There were also extensive soft tissue lacerations and bruising in the left calf. At the time of the injury preliminary débridement was carried out. The leg was placed in a plaster cast. The patient was extremely ill and numerous transfusions were given. There were several changes of plaster. After final removal of the cast, physiotherapy was commenced, consisting of massage, whirlpool baths, and baking. X-rays of the ankle showed typical spotty osteoporosis of the tarsal and metatarsal bones. The ankle was swollen and tender to palpation.

Fig. 4.—Comparative x-rays of the right hand. *A*, Showing osteoporosis, was taken one week prior to sympathectomy. *B*, showing almost normal calcification, was made four weeks after sympathectomy.

As time went on the patient continued to be unable to tolerate weight-bearing due to pain. It was noted that the foot was cold, moist, and blue, though arterial pulsations were present. There was limitation of motion of the ankle and foot in addition to the effect of the peroneal paralysis. One lumbar sympathetic block was done with an excellent response in the foot. In view of the long program ahead of this patient, including eventual dissection of the peroneal nerve, a left lumbar sympathectomy was done on Feb. 14, 1944. The response to operation was most gratifying and achieved more than had been hoped for. Subjective improvement in ankle comfort was marked. In about two weeks partial weight-bearing was commenced. Calcium deposition was noted in the bones of the foot. The patient was transferred to a neurosurgery center.

CASE 4.—Aug. 4, 1944, near St. Lo, a 33-year-old private first class received a gunshot wound of the left foot, with fractures of the os calcis, cuboid, navicula, and shafts of the second, third, and fourth metatarsi. After initial débridement and application of a cast he was evacuated to England, where pulp traction was applied to the second, third, and fourth toes. Traction was maintained for six weeks. On Sept. 1, 1944, a new cast was applied. At this time the wounds were entirely healed. He was admitted to this hospital Nov. 9, 1944, wearing a cast. The patient was given a weight-bearing cast, but the ankle continued to be painful. X-rays (Fig. 7) showed a persistence of marked osteoporosis of the distal tibia, tarsi, and metatarsi. On Feb. 22, 1945, the cast was removed and active physiotherapy started, consisting of paraffin and whirlpool baths. The patient was encouraged to walk up to three

Fig. 7.—Extreme osteoporosis is shown eight months after the original injury; the upper picture shows some of the old fractures.

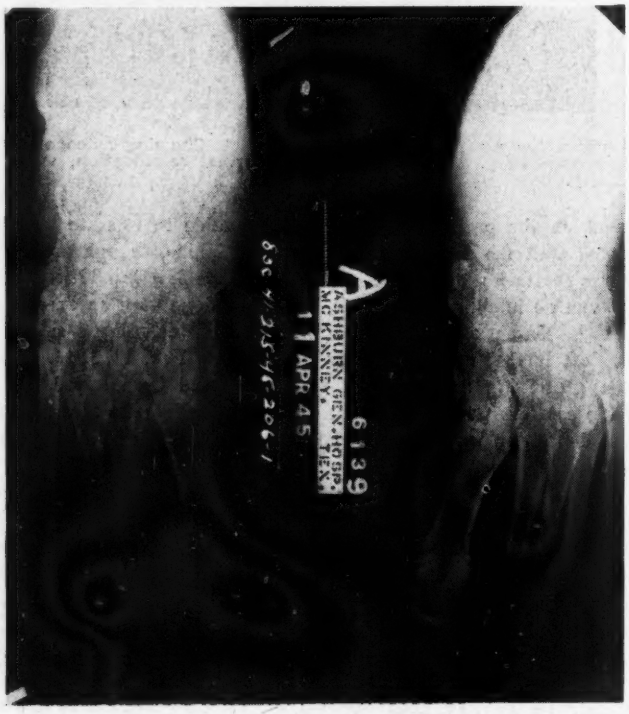

Fig. 8.—X-ray views taken after five lumbar blocks over a period of three weeks showing diminution of osteoporosis; patient's foot is now comfortable and he is ambulatory without support.

Fig. 5.

Fig. 6.

Fig. 9.

Fig. 10.

Fig. 5.—The scar and deformity of the thumb are shown, with marked discoloration of the thumb and dorsum; the thumb nail has been allowed to grow because of pain caused by trimming it.

Fig. 6.—Comparison of both hands shows the shiny atrophic condition of the skin of the left hand, together with color changes.

Fig. 9.—The scarring of the right palm and discoloration of right hand are shown.

Fig. 10.—The dorsum of the right hand and fingers is swollen; there is an ulcer of the nail bed on the fourth finger.

miles per day, but pain was still present and there was swelling of the ankle. No improvement in the osteoporosis was noted. The foot was cold, blue, and usually moist. Occasionally it became warmer than its mate, although at such times it had a dusky hue. March 22, 1945, a series of novocain blocks was instituted. After the first block the patient was subjectively improved and could walk much better. The foot remained warm and dry for about twenty-four hours. After five blocks the appearance of the soft tissues and the patient's ability to walk were sufficiently improved to justify a period of observation. X-rays taken at this time, three weeks after the first block, showed greatly diminished osteoporosis (Fig. 8).

CASE 5.—A private first class, 30 years of age, was admitted to the hospital in August, 1944. His transfer diagnosis was trench foot and, on questioning, it was learned that this soldier had been fighting for a period of thirty days in the cold mountainous area of Italy without removing his shoes and stockings. The immediate course was typical of trench foot with marked swelling of the feet, bleb formation, and pain. The residual symptoms consisted of the usual pain on weight-bearing, but he had marked tingling and showed irrefutable evidence of vasospasm of both feet. A novocain block on the right side on Sept. 15, 1944, caused the foot to become warm, pink, and dry for several hours and the patient was subjectively relieved for the same length of time. Nov. 13, 1944, a right lumbar sympathectomy was done. The response in the right foot was satisfactory and the patient was almost immediately relieved of the discomfort. He was insistent upon having the other side operated upon.

This, of course, is not the constant picture in the late stages of trench foot. The degree of vasospasm varies and not all cases are suitable for sympathectomy. Each case must be individualized, a period of physiotherapy tried, and test blocks of the sympathetic nervous system carried out. Two of our patients have had sympathectomies with complete relief of symptoms in each instance. One patient has returned to full duty and the other will probably do likewise.

When reconstructive surgery is indicated in the later repair of the effects of trauma, an adequate circulation is an essential in insuring good healing and function. Adequacy of the vascular bed is a prime requisite in all plastic procedures and it is probable that one should hesitate to perform an arthrodesis, bone graft, or other major procedure in an area where Sudeck's osteoporosis is marked and the soft tissues demonstrate the presence of severe vasospasm. It is a relatively simple matter to determine the effect of a temporary block before the reparative procedure is undertaken. Decision as to whether a series of novocain blocks before and after surgery or a permanent sympathectomy should be done will depend upon the adequacy of the response to one or two test blocks and upon the length of the reconstructive program which the patient is to undergo. In some instances it may be considered that the reconstructive surgery itself will release the vasospasm, as, for example, in amputation of a digit or release of scar tissue involving a peripheral nerve trunk. However, when a long plastic or orthopedic program is planned, particularly if prolonged immobilization of the extremity is necessary, sympathectomy is preferable to innumerable novocain blocks.

CASE 6.—A private first class, aged 25 years, cut his right hand in a crosscut saw in June, 1944, and sustained compound fractures of the phalanges of the third, fourth, and fifth fingers and laceration of the flexor tendons of all digits except the thumb. This resulted in extensive scar contracture of the palm of the right hand with limitation of flexion and extension of the fingers. On admission to this hospital in October, 1944, the hand was

deep red, cold, and clammy (Fig. 9). The patient complained that the hand was unusually sensitive to cold. It always felt heavy and clumsy. This sensation was increased on exposure to cold. The dorsum of the hand was slightly swollen and the normal creases on the extensor surface of the fingers were shallow. There was an ulcer at the nail margin of the right ring finger (Fig. 10). This began as a cigarette burn some days before and had failed to heal. There was anesthesia over the ulnar distribution on the fourth and fifth fingers. On his return from a thirty-day furlough there was no essential change in his condition. The cigarette burn had not healed.

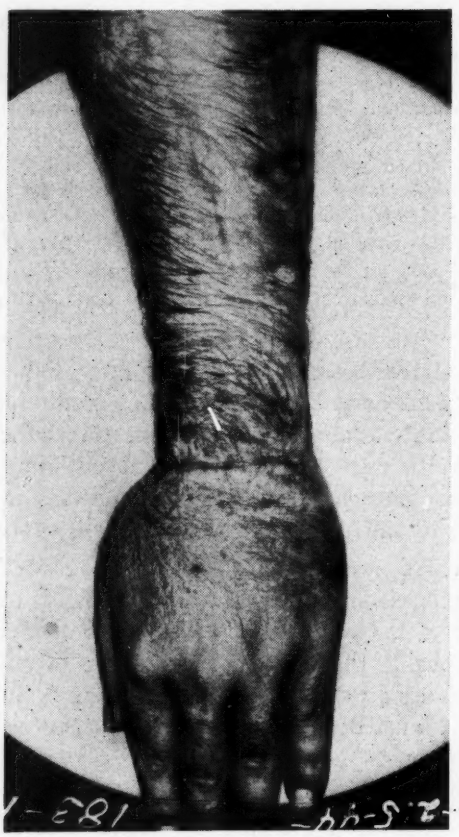

Fig. 11.—The transverse scar at the wrist and edema of the dorsum of the left hand are shown.

This patient was faced with an extensive reconstructive procedure on the hand entailing dissection of the palmar scar and skin graft. Nonhealing of the ulcer on the fourth finger could be attributed to "trophic" disturbances due to ulnar twig paralysis. However, the marked vasospasm seemed a more likely cause. A test block of the right stellate ganglion was done on Nov. 20, 1944, and the hand remained warm and dry for almost twenty-four hours. A second block, done on November 24, resulted in a permanent improvement of the hand. It remained warm and the discomfort lessened. The ulcer healed in about one week. It is felt that this patient was rendered a more suitable subject for plastic surgery. He was transferred to a hand center.

CASE 7.—A corporal received multiple wounds from an explosion of an aerial bomb in December, 1943. The chief injury was a transverse through-and-through wound of the extensor surface of the left wrist (Fig. 11). In its course the fragment severed most of the

extensor tendons and a sensory branch of the radial nerve. There were chip fractures of some of the metacarpi. There was a deep, firm cicatrix across the wrist with almost complete loss of motion at the wrist joint and complete loss of extension of the fingers. In addition, it was observed on admission at this hospital that the dorsum of the hand was edematous. The skin of the entire hand was blue, moist, and cold. The patient's discomfort was increased on exposure to cold.

Proper splinting and various modalities of physical therapy were carried out over a period of weeks in an effort to increase wrist motion and improve the circulation. There was no real improvement. It was obvious that extensive plastic repair of the wrist scar was indicated and that the extensor tendons would have to be repaired. The plastic procedure was advisable as the first step so that good tissues would be present for further reconstructive surgery on the tendons. Doubt was entertained as to the adequacy of the circulation in the recipient area to permit proper healing of the proposed pedicle flap. A dorsal sympathectomy was done in June, 1944, with an excellent effect on the circulation in the hand. The edema

Fig. 12.—Plastic surgery carried out after left dorsal sympathectomy; excellent healing resulted.

disappeared. Subjectively the patient's hand felt much better. During the following weeks function improved at the wrist. A pedicle from the abdomen was transferred to the wrist by Major Kerwin Marcks and excellent healing resulted (Fig. 12). The patient was transferred to a hand center for further reconstructive surgery. A letter from this patient states that he now has almost complete use of the fingers.

Sympathetic block or sympathectomy when the main arterial supply of an extremity has been interrupted has saved many limbs. Due to the conditions which often are present at such time, it is usually better to institute novocain blocks immediately and await stabilization of the patient's condition before contemplating sympathectomy. The latter procedure may not even be necessary to prevent gangrene if blocks are carried out early and often.

CASE 8.—In June, 1944, a sergeant, 29 years of age, sustained a shell fragment wound of the left femoral artery 5 cm. above the level of the knee joint. The artery and vein were ligated and a series of lumbar sympathetic blocks was immediately instituted and continued over a period of days. For five days amputation seemed imminent, but collateral circulation developed and no actual gangrene occurred. On admission to this hospital in September, 1944, the patient had a rather marked limp and complained of weakness and numbness in the left leg and foot. There were no striking color changes in the left foot but it was cooler than the right and there was considerable atrophy of the calf. There was definite weakness of the calf muscles. After a thirty-day furlough there was no change in the patient's condition. Mecholyl iontophoresis was given three times a week without benefit. In September, a left lumbar sympathetic block produced a striking improvement of the circulation in the foot. In October, a left lumbar sympathectomy was done. There was an immediate improvement in the patient's subjective sensations in the leg. Strength returned rapidly in the next few weeks and the patient was returned to full duty.

Fig. 13.—The mummified condition of the left foot is shown. There are ischemic ulcers at the tips of the first and third toes.

CASE 9.—In February, 1944, a private received a perforating wound of both thighs and right knee from artillery fragments. The left popliteal artery was severed. Emergency surgery was carried out almost immediately with ligation of the left popliteal artery. No sympathetic blocks were performed. Two days later a left lumbar sympathectomy was done. Dry gangrene developed, involving the tips of the first, second, and third toes and all of the fourth and fifth toes. The fourth and fifth toes were amputated in June in the United States. On admission of the patient to this hospital the left foot looked almost mummified. There was atrophy of the skin and subcutaneous tissue and the forefoot and toes were stiff (Fig. 13). There were chronic ischemic ulcers of the first and third toes. The foot, however, was warm and dry. After a period of treatment with paraffin and galvanic baths there was practically no improvement, and the patient was transferred to an amputation center for evaluation. Maximum vasodilatation had been achieved in this case by the sympathectomy.

The inclination is to believe that the two-day interval between the injury and the sympathectomy may explain the gangrene, since it is likely that in this time there was enough

damage to the soft tissues of the foot from ischemia so that arteriolar dilatation, when achieved, was too late. Of course, it is possible that without sympathectomy in this case more tissue would have been lost than will now be the case.

Some interest has recently been aroused in the possibilities of subjecting acute injuries of the extremities to early sympathetic interruption, usually by novocain block, the rationale in this treatment being the immediate improvement in the circulation with resultant reduction of edema and an earlier return of the soft tissues to a normal state. The delayed effects of such therapy have yet to be evaluated, but it is entirely possible that the disability from crushing injuries about the wrists and ankles may be reduced due to an early lessening of edema and prevention or lessening of osteoporosis. The boggy, cold, and painful ankle which follows a Pott's fracture is well known. Disability of twelve to fourteen weeks or longer is anticipated with this fracture, due not so much to failure of bony union as to soft tissue changes with mild or severe vasospasm and osteoporosis of varying degrees, with pain and swelling on weight-bearing.

Work along this line was carried out in a neighboring station hospital where many acute injuries were seen. The results of this investigation will undoubtedly be reported in the near future. From our own small series of acute injuries treated in this manner, two representative cases are presented here for illustration.

CASE 1.—A private, 26 years of age, was admitted to the hospital on April 1, 1945, having sustained a fracture of the right ankle eight hours previously. He had walked about one-half mile after the accident and at the time of entry there was brawny edema of the foot and ankle and pronounced ecchymosis. X-rays revealed a fracture of the tip of the external malleolus and two fractures of the tibial malleolus. A satisfactory block of the left lumbar ganglia was obtained and as soon as vasodilatation occurred the patient found that he could voluntarily move his ankle in all directions without pain. Painless reduction of the fracture was obtained without further anesthesia and a nonpadded cast was applied. On the following morning, thirty-six hours after the injury, there was wrinkling of the toes, indicating a lessening of edema. Three subsequent daily lumbar blocks were performed. One week after the injury the cast seemed somewhat loose and it was, therefore, removed. The ecchymosis was still severe, but in other areas the edema of the foot and ankle was greatly reduced.

CASE 2.—A sergeant from the reconditioning section sustained a severe sprain of the right ankle on April 5, 1945. There were swelling and ecchymosis about the external malleolus and the patient was unable to bear his full weight on this side. A lumbar sympathetic block was performed and there was immediate reduction of pain. He was able to walk without help. An elastic bandage was applied and the patient told to remain in quarters. Two hours later, however, he engaged in a game of baseball and played five innings.

For full evaluation of the results of this treatment in such cases, a prolonged follow-up of numerous cases is necessary. It is conceivable, especially in the fracture cases, that, in addition to the immediate improvement in discomfort and swelling, some of the late effects may be avoided. There might be a lessening of osteoporosis and vasospasm in the later course which would result in an earlier resumption of function.

SUMMARY AND DISCUSSION

Novocain block of the sympathetic outflow and permanent sympathectomy have been discussed in relation to three main categories of post-traumatic conditions, comprising:

(1) Post-traumatic painful and vasospastic states with or without Sudeck's painful osteoporosis. In this group are included those patients needing reconstructive surgery in an area where the circulation is dangerously decreased.

(2) Injuries of the main arterial supply of an extremity.

(3) Acute injuries, particularly fractures and crushing injuries of the hands and feet.

Illustrative cases in all three groups are described where some form of sympathetic interruption was carried out. It is pointed out that a large percentage of patients who have sustained injuries of the extremities have prolonged pain and disability, often associated with vasospasm and osteoporosis, and that in these individuals permanent or repeated temporary interruption of the sympathetic outflow often results in a reduction in discomfort, malfunction, and prolonged hospitalization. Where extensive plastic or orthopedic procedures are contemplated, vasospasm and severe osteoporosis should be corrected prior to reconstructive surgery. Though application of these principles *early* in the presence of acute injuries of the hands and feet has not been given extensive trial, there is reason to believe that a reduction of both the early and late results of trauma to the soft tissue and bone may be achieved by sympathetic paralysis.

In view of the large proportion of individuals who show vasospastic changes after trauma of the extremities, it behooves the medical profession to be on the alert to discover and treat these manifestations.

After prolonged immobilization of an extremity in plaster there is usually a diminution of the blood supply, resulting in a cold hand or foot. The extremity may also show varying degrees of cyanosis. If this condition does not improve promptly in three or four days of active physical therapy, one novocain block of the appropriate sympathetic fibers may suffice to relieve the condition. If, however, the condition returns and vasospasm is clearly present, particularly if accompanied by osteoporosis, a series of blocks should be given, making one or two injections per week. If sufficient permanent improvement does not result after five or six blocks, and if there is the usual pain and swelling on weight-bearing, much valuable time will be saved if a permanent sympathectomy is performed. This is done only if the test blocks have been shown to give temporary relief.

Probably a reduction of disability could be achieved if vasospasm and osteoporosis were looked for during the period of immobilization and blocks carried out where indicated.

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ABDOMINAL APOPLEXY SECONDARY TO RUPTURED "CONGENITAL" ANEURYSM

Multiple Aneurysms of the Inferior Pancreaticoduodenal Artery With Rupture of One

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THE spontaneous rupture of a medium-sized intra-abdominal blood vessel independent of trauma, malignant tumor, or ectopic gestation has been termed "abdominal apoplexy." Although the rupture of an arteriosclerotic vessel is the usual cause of this rare condition, Bruce[1] in 1937 suggested that the rupture of a small "congenital" aneurysm might be responsible in some cases, particularly in the earlier age groups. Schuster[2] (1937) shortly thereafter described multiple aneurysms of the splenic artery which she believed were of congenital or developmental origin in a case of familial hemorrhagic telangiectasia. Nevin and Williams[3] (1937) described a case of massive spontaneous intraperitoneal hemorrhage due to rupture of a "congenital" splenic aneurysm associated with multiple aneurysms of the branches of the circle of Willis. It is the purpose of this paper to report another case, which by its instructive histologic picture adds further support to the concept of aneurysm secondary to congenital defect in the arterial wall, and to discuss the recent literature on this subject.

CASE REPORT

J. O., a white man, aged 50 years, was admitted to the ward surgical service of the Jefferson Medical College Hospital on Dec. 25, 1943, with the chief complaint of epigastric pain.

For the past several years the patient had occasionally experienced a burning sensation in the epigastrium about two hours after eating, relieved by the taking of alkali. At 8 P.M. on Dec. 24, 1943, he experienced sudden, moderately severe, continuous, epigastric pain radiating straight through to the back, associated with slight nausea. The pain persisted throughout the night, preventing sleep. The following morning he drank a glass of milk which was promptly vomited. Because the pain failed to subside he made his way to the hospital at noon and upon arriving grew faint and collapsed, but did not lose consciousness.

Systemic review, past medical history, and family history contributed nothing of significance.

Physical Examination.—The patient appeared apprehensive, pale, and slightly cyanotic. The skin was cold and clammy. Temperature was 97° F.; pulse, 120; respirations, 26; blood pressure, 70/40. The pupils were of equal size and reacted to light and accommodation. The heart and lungs were essentially normal. On abdominal examination there was no limitation of diaphragmatic excursions. There was moderate tenderness, but no rebound tenderness, in the epigastrium and slight upper rectus muscle guarding. Peristalsis was normal. Rectal examination was negative. The extremities were normal.

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The clinical diagnostic impressions on admission were penetrating peptic ulcer or acute pancreatitis.

Laboratory Studies.—Hemoglobin was 84 per cent; red blood cells, 4,100,000; white blood cells, 13,400; color index, 1.02. Urinalysis was normal. Wassermann and Kahn serologic studies were negative. The blood urea nitrogen was 14.0 mg.; sugar, 73 mg.; serum proteins, 5.2 Gm.; and serum amylase, normal. A plain roentgenogram of the abdomen was normal.

Further Progress.—Following the intravenous administration of concentrated plasma and fluids, the patient's condition improved and the blood pressure rose to 120/90. Wangensteen suction was instituted. The pain diminished, at no time requiring medication for relief, and the abdominal tenderness and muscle guarding gradually subsided. Because of the marked improvement, conservative therapy was continued. The following day the temperature was normal; pulse, 100; hemoglobin, 71 per cent; red blood cells, 3,500,000; and white cell count, 9,000. At this time 500 c.c. of whole blood were administered. The patient continued to improve, was pain-free, and except for a fluctuation of temperature between normal and 101° F. appeared to be in excellent condition.

Fig. 1.—Gross specimen, showing the superior mesenteric and inferior pancreaticoduodenal arteries. Arrows point to the ruptured saccular aneurysm at the first bifurcation. Note the extravasated blood in the vicinity of the vessels.

At 9 P.M. on Dec. 29, 1943, the patient again complained of epigastric pain accompanied by a feeling as if something had broken, and went into the same shocklike state as on admission. Blood count at this time revealed a hemoglobin of 71 per cent; red blood cells, 3,000,000; and white cells, 12,000. The sedimentation rate was 36 mm. within forty-five minutes. The pulse was 120, blood pressure, 94/60, and the abdominal findings as on admission. He again improved following the administration of plasma and fluids intravenously. It was thought at this time that the patient might have a dissecting aneurysm of the abdominal aorta. At 6 A.M. on Dec. 30, 1943, he again went into shock and died.

Post-mortem Examination.—

Gross: The peritoneal cavity contained approximately 1,200 c.c. of fluid and clotted blood. In addition, there was extensive hemorrhage into the retroperitoneal tissue of the

upper abdomen, particularly into the pancreas, transverse mesocolon, and around the upper portion of the aorta and right kidney. The head of the pancreas contained the greatest amount of hemorrhage and was partially destroyed by it.

The inferior pancreaticoduodenal artery, arising from the superior mesenteric, pursued a normal course for 3 cm. until its first bifurcation. At this point there was a sacculated aneurysm about 4 cm. in diameter, the ostium of which measured 1 cm. in length and 3 mm. across (Fig. 1). It was filled with a gray, laminated, antemortem clot and was in direct communication with the hemorrhagic material distributed throughout the pancreas and elsewhere. In the peripheral portion of the same artery there were three fusiform dilatations, not in relation with bufurcation angles. The lumens of two of these were ragged and contained antemortem blood clot. The remainder of the mesenteric artery, the celiac axis with its branches, and the portal vein were normal.

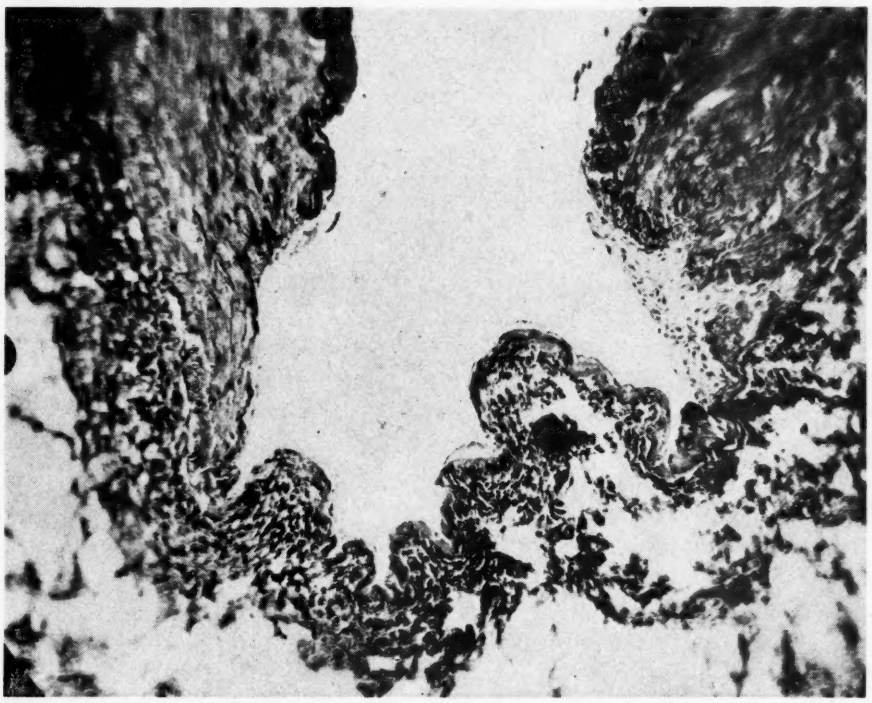

Fig. 2.—Inferior pencreaticoduodenal artery distal to the ruptured saccular aneurysm, showing a defect in the intima, internal elastic lamina, and all but the outer portion of the media. Note the partial covering of the inner portion of the media to the right by the internal elastic lamina, the presence of a few elastic fibrils in the floor of the defect, and the absence of inflammation in the adventitia and surrounding tissue. Elastic tissue stain with van Gieson counterstain (×100).

The aorta and pulmonary vessels contained a smooth glistening intimal surface throughout. The heart was essentially normal and the coronary arteries showed moderate arteriosclerosis but no occlusions. The basilar vessels of the brain did not show any atherosclerosis or small aneurysms.

Histologic Examination: The entire inferior pancreaticoduodenal artery was blocked and several sections taken from each block. They were stained with hematoxylin and eosin and with Weigert's elastic tissue stain, using picric acid and acid fuchsin as counter stain. In the following description they are considered in the order in which it is thought the lesions evolved.

Sections of the main portion of the vessel just beyond the large aneurysm disclosed a small defect in the intima, internal elastic membrane, and all but a small rim of the outer

portion of the media (Fig. 2). One side of the defect showed a gradual attenuation from within out, while the other was more abrupt. The inner half of the media of the latter was covered with both the intima and the internal elastic membrane. The outer half of the media on this side was covered with a few edematous fibroblasts. Only a fraction of the inner portion of the media on the opposite side of the defect was covered with the internal elastic membrane. The rest was bare. The floor and base of the defect consisted of a very thin strip of the outer portion of the media in which there were a few elastic fibers. The adventitia and surrounding connective tissue were normal, showing no inflammation or hemorrhage. In the outer quarter of the media on each side of the defect there was some erythrocytic extravasation. Elsewhere the media and the remaining coats of the vessel were normal.

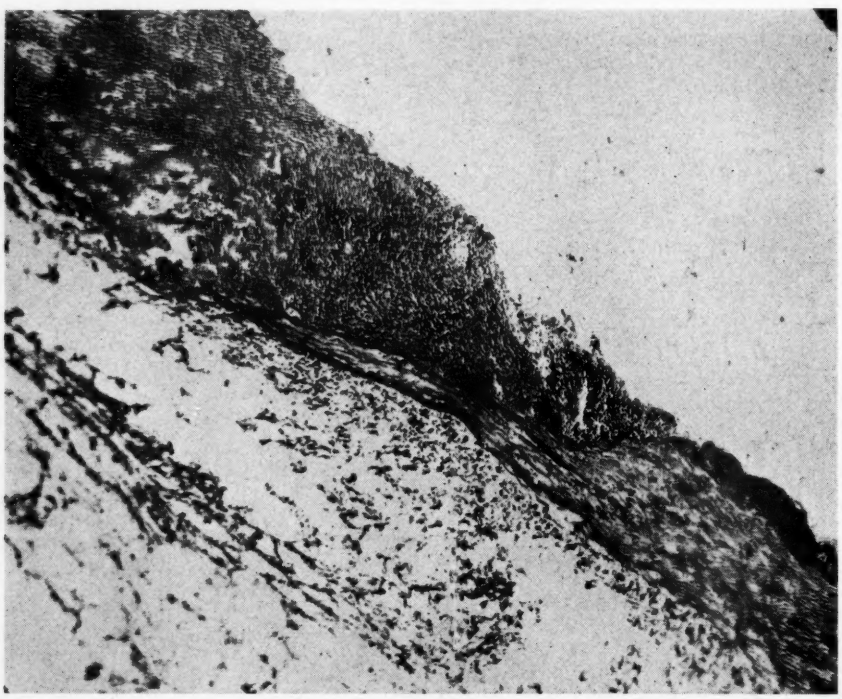

Fig. 3.—Section of one of the distal aneurysmal dilatations, showing a sudden termination of the intima and internal elastic lamina and a gradual attenuation to complete disappearance of the media. The floor of the defect is filled with recently coagulated blood. Elastic tissue stain with van Gieson counterstain (×50).

In another area there were two similar but more superficial and saucerlike defects in the vessel separated from each other by a small island of relatively normal wall. These defects differed from the former in that (1) the walls showed a more gradual slope, (2) the outer third of the media was still intact and formed the floor, and (3) the adventitia and surrounding connective tissue were replaced with recent granulation tissue composed of fibroblasts, capillaries, and varied numbers of plasma cells, lymphocytes, and polymorphonuclear leucocytes. Further out there was extensive extravasation of erythrocytes.

The walls of the distal aneurysmal dilatations were similar to those previously described with the exception that in each the edges of the defects were widely separated; all the media had disappeared and the concavity was filled with varying amounts of recently coagulated blood (Fig. 3).

The wall of the aneurysm at the first bifurcation disclosed a sloping defect in its coats similar to those already described. This gradually disappeared in a mass of extravasated

blood. Sections of the wall of the peripheral portion of this aneurysm disclosed no remnants of a vessel. They were composed of extensive erythrocytic extravasation throughout the fat and connective tissue with only occasional islands of granulation tissue. Sections of other vessels in the vicinity of this pancreaticoduodenal artery and of the inferior pancreaticoduodenal artery in twelve consecutive autopsies disclosed no pathologic changes.

DISCUSSION

Although grossly the only changes seen in the artery were a ruptured saccular aneurysm at the first bifurcation and three small fusiform dilatations in the more distal portions of the vessel, the microscopic sections disclosed a defect along its entire course. The many sections furthermore showed various degrees of involvement and so permitted the following reconstruction of the probable train of events. Originally there was a congenital or developmental defect along the entire course of the artery consisting of what appeared to be a complete or partial failure of fusion of the media. At first this defect was most likely covered on its inner surface with the internal elastic membrane and the intima, but as the vessel was stretched these coats were broken, leaving a portion of the media and the adventitia or in some areas the adventitia alone to form the entire remaining wall. That the internal elastic membrane and the intima did at one time cover the defect is given some support by finding the former still covering a portion of the defect in some of the sections (Fig. 2). Where the dilatation of the artery was minimal, as in the distal three aneurysms, the defects were filled with recently coagulated blood. Where the dilatation was so great as to cause a complete break in the adventitia, as in the aneurysm at the first bifurcation, there was massive hemorrhage not only into the immediately adjacent tissue and along the vessel but throughout the retroperitoneal space. The onset of the hemorrhage was apparently coincident with the first attack of pain about five and one-half days before death. Proof of this is seen in the recent periarterial granulation tissue observed in most of the sections.

Aneurysms of branches of the abdominal aorta, regardless of type, are rare. From the literature and their own experience, Malloy and Jason[4] (1942) collected eighty-five cases of hepatic artery aneurysm; Machemer and Fuge[5] (1939), eighty-four cases of the splenic; and Lowsley and Cannon[6] (1943), seventy-five cases involving the renal artery. Single and multiple aneurysms unassociated with inflammatory or degenerative change have been reported, but only in the cases of Schuster[2] and Nevin and Williams[3] was a medial defect at the bifurcation angle described. On the other hand, intracranial aneurysms, most frequently the so-called "congenital" type, are found in 0.8 per cent of all post-mortem examinations according to Fearnsides[7] and in 1.5 per cent according to Schmidt.[8]

The concept that single or multiple aneurysms might in some instances be due to a congenital defect in the arterial wall was first introduced by Eppinger[9] in 1887. This concept was investigated by Forbus[10] (1930), who demonstrated the association of miliary aneurysms of the superficial cerebral vessels with a characteristic defect in the tunica media at the angle of bifurcation of the arteries. This muscularis defect was shown to date from embryonic life. During development, the main trunk of the vessel receives its muscular coat at an

earlier period than the branches. The corresponding coat of the branch is then formed not as a direct extension from the parent trunk, but separately as a condensation from the surrounding mesenchyme. Fusion of the coats at the angle of origin of the branch may be faulty and thus result in an area of congenital focal weakness in the vessel wall. Forbus did not conclude that the aneurysm in its fully developed state is a congenital malformation per se, but an acquired lesion arising from a combination of focal weakness in the arterial wall on the basis of a congenital muscular defect, and degeneration of the internal elastic membrane as the result of continued overstretching of this membrane.

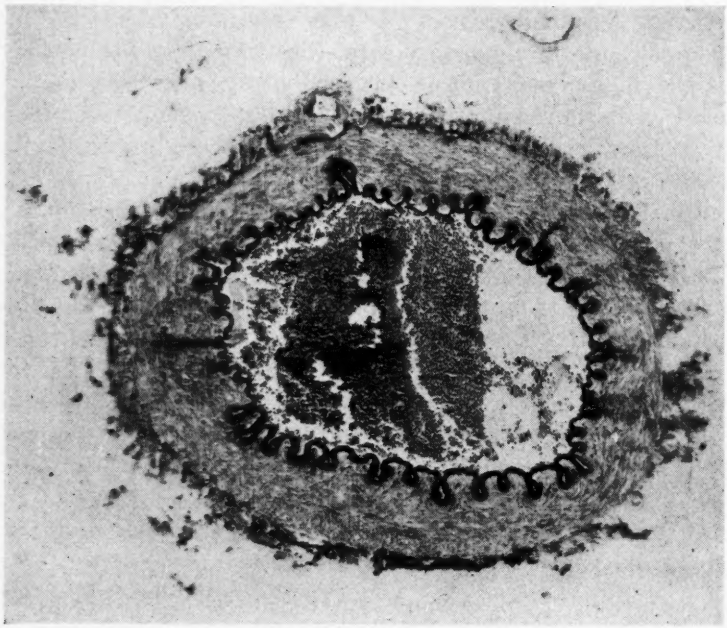

Fig. 4.—Section of a cerebral artery, showing the elastic tissue almost entirely concentrated in the internal elastic lamina. Elastic tissue stain with van Gieson counterstain (×50).

Developmental defects of the media at the angles of arterial bifurcation are relatively frequent in cerebral, coronary, pulmonic, abdominal, and other medium-sized vessels, but the incidence of associated aneurysms is greatest by far in the cerebral ones. Glynn[11] (1940) stated that in thirty-seven out of forty-seven nonaneurysmal cases (approximately 80 per cent) there was a defect in the media at the angle of bifurcation of cerebral vessels, and he therefore questioned the etiologic relationship between these defects and aneurysms. He attempted to demonstrate by means of simple inflation experiments with vessels bearing natural or artificial medial defects that the internal elastic lamella is of greater relative importance in maintaining the form of the cerebral arteries. He concluded that the greater frequency of these aneurysms in the circle of Willis must be due to a difference in the topography of the elastic tissue of these vessels. According to this author as well as others (Hackel,[12]

Cobb and Blain[13]), in cerebral vessels almost the whole of the elastic tissue is concentrated in the internal elastic lamina (Fig. 4), and by reason of this position is probably more susceptible to injury and degeneration than if it were more widely distributed through the media and adventitia as in other vessels (Fig. 5).

Richardson and Hyland[14] (1941) in an exhaustive study of intracranial aneurysms stated that the medial defects are probably developmental and play a role in the formation of aneurysms, but that there is in addition an unrecognized acquired lesion causing degeneration of elastic tissue. They conclude that at present complete knowledge as to the cause of these aneurysms, frequently referred to as "miliary," "berry," "bifurcation," "congenital," or "developmental," is lacking.

Fig. 5.—Section of a mesenteric artery, showing the elastic tissue concentrated in the internal and external elastic lamina, and also dispersed throughout the media. Elastic tissue stain with van Gieson counterstain (×50).

The case of Nevin and Williams[3] represents the first in the literature in which massive intraperitoneal hemorrhage is reported secondary to rupture of an aneurysm of an intra-abdominal vessel associated with a defect in the medial coat at the bifurcation angle. The present report represents a second case in which the aneurysm may be designated as "congenital" or developmental because of its multiplicity, location at the bifurcation angle of a medium-sized artery, small size, and association with a defect of the muscularis.

The case of Budde,[15] in which bleeding occurred from a side branch of the left gastroepiploic artery, must be excluded from the group under dis-

cussion since no definite aneurysm was visualized, a section of the vessel was not removed, and the cause was undetermined. The only reference we could find to aneurysms of the inferior pancreaticoduodenal artery was that of Bortolozzi[16] who described an unruptured fusiform arteriosclerotic aneurysm of this vessel discovered post mortem in a patient who died of carcinoma of the head of the pancreas.

The clinical features of abdominal apoplexy have recently been reviewed by Berk, Rothschild, and Doane.[17] Their analysis of twenty cases revealed nothing pathognomonic in either the symptoms or signs that would permit the diagnosis with certainty. The usual findings consist of abdominal pain, signs of peritoneal irritation, and the general manifestations of internal hemorrhage. All these features were present in our case, but the lesion was not diagnosed, since the possibility of its existence was not considered. Ligation of the bleeding point was employed in 80 per cent of this series, with recovery in 69 per cent. The prognosis is excellent if a definite bleeding point can be found, since in no case was there a recurrence reported following operation.

SUMMARY

1. A case of abdominal apoplexy secondary to rupture of one of multiple "congenital" aneurysms of the inferior pancreaticoduodenal artery is reported.

2. A "congenital" aneurysm is characterized by its frequent multiplicity, small size, location at the bifurcation angle of a medium-sized artery, and association with a defect in the muscularis.

3. The clinical features consist of abdominal pain, signs of peritoneal irritation, and the general manifestations of internal hemorrhage.

CONCLUSIONS

1. Massive intraperitoneal hemorrhage resulting from the rupture of "congenital" aneurysms of branches of the abdominal aorta is exceedingly rare in comparison to the analogous condition in cerebral arteries.

2. The rupture of a "congenital" aneurysm should be suspected when abdominal apoplexy occurs in patients without marked arteriosclerosis or hypertension.

3. Early operation, with excision of the aneurysm, would seem to offer the best chance of recovery.

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PENICILLIN THERAPY OF INFECTIONS IN 220 PATIENTS*

A Clinical and Bacteriologic Study

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THIS report covers the initial period of penicillin investigation (exclusive of sulfa-resistant gonorrhea in the male) at Walter Reed General Hospital from July, 1943, through September, 1944. The cases that form the basis of this report were, with a few exceptions, personally supervised by the Penicillin Committee.

DOSAGE

The sodium salt of penicillin has been used for the greater part in this study. The calcium salt was employed for a time in a few patients but no clinical difference between the two was detected.

We have used relatively large dosages, as our primary aim has been to explore the power of penicillin rather than its minimal effective amount. Among the susceptible bacteria, gonococci, streptococci, and pneumococci will almost always respond to 90,000 to 100,000 units a day or less. Staphylococci, the most important surgical bacteria, vary so widely in susceptibility to the drug (Fig. 1) that we have come to start off with 120,000 to 200,000 units a day and will not abandon penicillin in a serious infection until one-half million units a day prove ineffective. The anaerobic clostridia and actinomyces are apparently even more resistant than are the staphylococci. Bloomfield, Kirby, and Armstrong[1] pointed out the danger of inadequate dosage or of stopping treatment too soon, and Harford and co-workers[2] described a severe case of osteomyelitis of the ilium responding to massive dosage when the usual doses were ineffectual.

Several times in our experience large dosages of penicillin succeeded where standard ones were failing: a sycosis vulgaris of mixed streptococcus and staphylococcus culture, a staphylococcal cavernous sinus thrombosis, and a severe staphylococcal wound infection all unimproved by 90,000 to 120,000 units a day yielded to 360,000 units a day. A recent patient, not of this series, with staphylococcal perichondritis of the lower left ribs and early osteomyelitis of the sternum grew progressively worse in spite of radical surgery and 200,000 units a day. Increasing the penicillin to 520,000 units daily dramatically halted the process which has now been soundly healed over three months.

ROUTES OF ADMINISTRATION

The great majority of our patients have been treated by intramuscular injections at three-hour intervals. A drop of 2 per cent novocain in each cubic

Technician (4th Grade) George E. Rittman, Miss Dorothy Talbott, and Technician (5th Grade) Mina Levy rendered valuable technical assistance.

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centimeter of the penicillin solution renders the injections almost painless. One of us (M.R.)[3] has developed a suspension of calcium penicillin in beeswax peanut oil which will maintain therapeutic blood levels for an eight-hour period after a single injection. Trumper and Hutter[4] have attained a similar effect by applying an icecap to the site of injection.

A few patients in this series received the agent either by constant intravenous or constant subcutaneous drip.[5] The latter route proved valuable in treating a small girl with osteomyelitis of the femur who would not tolerate repeated intramuscular injections. It is our clinical impression as well as that of others[5-7] that the same amount of penicillin is slightly more effective when given by intravenous drip than by intramuscular injection. The highest blood levels are also obtained by this method.

Local application of penicillin in a saline compress or water soluble ointment may be employed to advantage to infected granulation tissue and cavities. We have found that in an Aquafor base, penicillin activity persists for at least twelve hours in infected wounds.

Since blood-borne penicillin will not reach the meninges in therapeutic quantities and since only a fraction of the blood level penetrates the serous cavities, local injection of the drug is important in treating infections in these locations.

Except in infections of the meninges and serous spaces, the parenteral route of penicillin administration seems to be unquestionably superior to the local, but in wounds which are sufficiently open to allow thorough local permeation, the local application will enhance the general effect of the drug and in certain cases will be sufficient of itself to control infection.

COMPLICATIONS

In our entire series of patients no complications of more than nuisance value could be ascribed to the penicillin. Three debilitated patients developed deep femoral thrombosis during or just after penicillin therapy. It is doubtful whether this should be blamed upon the drug, especially since repeated observations of bleeding and clotting times and prothrombin times of a number of patients under treatment failed to reveal any clotting tendency. Mild thrombophlebitis at the site of constant intravenous injection will frequently occur, especially when higher concentrations of penicillin are administered, but this rapidly subsides upon discontinuance of the infusion, and it will not be reactivated by continued injection at another site.

Local pain at the site of injection has nearly been eliminated by purification of the agent and by the addition of novocain to the diluting solution as described.

Urticaria lasting three to six or seven days is the commonest of all the untoward reactions to penicillin but we have never been compelled to stop treatment on this account. In addition there were other infrequent reactions including angioneurotic edema, nausea and vomiting, unpleasant flushing and precordial oppression, diarrhea, etc.

LABORATORY DATA

Methods.—An attempt was made to maintain a uniform laboratory approach throughout the study. Standardized procedures were established for obtaining and processing the cultures and samples of body fluids. Specimens were obtained at the bedside where they were inoculated directly into thioglycolate broth with .1 per cent dextrose and streaked on blood agar (veal infusion agar base with 10 per cent horse blood). If anaerobic infection was suspected a tube of Robertson's cooked meat medium was also inoculated. After fourteen to eighteen hours of incubation, plates were read and definitive identification was carried out including carbohydrate fermentations, determination of coagulase activity, and Lancefield grouping of the beta hemolytic streptococci.* Determination of penicillin sensitivity of organisms was according to the method of Rammelkamp and Maxon.[8] Penicillin assay of body fluids, urine, and exudates was performed by Rammelkamp's procedure.[9]

Penicillin Sensitivity of Organisms.—Fig. 1 shows the range of in vitro sensitivity to penicillin of the eighty-six strains of staphylococci, thirty-three strains of beta hemolytic streptococci, and forty-two strains of alpha and nonhemolytic streptococci so tested. Sixty-two of the staphylococci strains demonstrated plasma coagulation. Of the beta hemolytic streptococci, eight strains were Lancefield Group A, one Group B, one Group C, eleven failed to react to serums for Groups A, B, C, D, E, F, H, and L, and eleven were not tested.

Among the miscellaneous bacterial flora were ten strains each of pneumococcus and *Streptococcus faecalis;* the former were sensitive from .04 to .0025 Oxford units; the latter from 1.42 to 5.71 units. Faecal streptococci thus appear as organisms which would not be influenced by blood levels ordinarily obtainable by parenteral therapy.

Three strains of *Actinomycosis bovis* isolated from human beings were examined. Two of the strains were inhibited by 0.25, the third by 1.0 Oxford unit per cubic centimeter.

Development of Increased Resistance in Vivo.—There were only three strains of staphylococci in which development of resistance in vivo to penicillin was conclusively demonstrated. Two of the organisms were isolated from patients with cellulitis and exhibited approximately a thirty-five-fold increase in resistance in two and five days, respectively. The patients during this period were receiving 30,000 units of penicillin every three hours intramuscularly. In both instances the clinical response was excellent. The third strain was isolated from a patient with an infected amputation stump receiving 120,000 units daily by the intermittent intramuscular method. Despite the appearance in four days of a threefold increase in resistance of the organism, this patient's response to treatment was considered satisfactory. The beta hemolytic streptococci, with their greater sensitivity to penicillin, were more uniformly responsive to therapy. There were no instances of in vivo increased resistance developing in this group of organisms.

*Lancefield grouping was performed in the Division of Bacteriology, Army Medical School.

Penicillin Levels in Blood, Pleural, and Spinal Fluids.—Blood levels determined from time to time upon patients receiving penicillin at three-hour intervals by intramuscular injection and by constant intravenous and subcutaneous drip were comparable to those reported by others.[1, 10, 11]

The instillation of 40,000 units of penicillin intrapleurally in cases of empyema yielded levels of 2.5 to 9.9 Oxford units per cubic centimeter in the pleural fluid twenty-four hours later and therapeutic amounts of the agent persisted for five days after the initial instillation. Intramuscular injections of

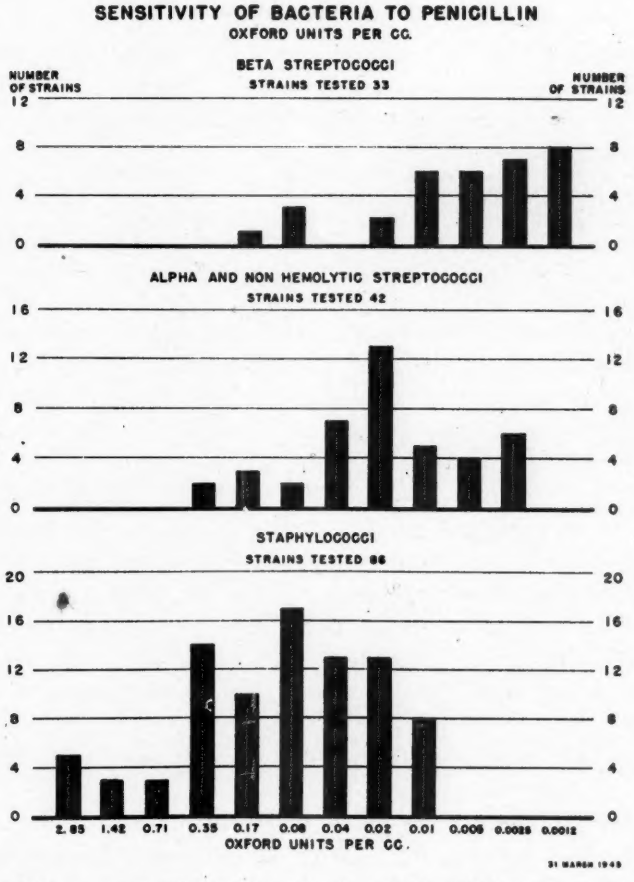

SENSITIVITY OF BACTERIA TO PENICILLIN
OXFORD UNITS PER CC.
BETA STREPTOCOCCI
STRAINS TESTED 33
NUMBER OF STRAINS
ALPHA AND NON HEMOLYTIC STREPTOCOCCI
STRAINS TESTED 42
STAPHYLOCOCCI
STRAINS TESTED 86
2.85 1.42 0.71 0.35 0.17 0.08 0.04 0.02 0.01 0.005 0.0025 0.0012
OXFORD UNITS PER CC.

Fig. 1.—Sensitivity to penicillin of streptococci and staphylococci from present series.

60,000 units of penicillin at three-hour intervals produced levels of .156 to .312 units per cubic centimeter in a tuberculous pleural effusion. However, in the pus of established empyemas, intramuscular dosages of 25,000 units every three hours achieved insignificant penicillin concentrations (0 to .078 Oxford units).

Spinal fluid assays in ten patients undergoing parenteral therapy up to 480,000 units a day for other than central nervous system infections revealed the merest traces of penicillin. On the other hand, intrathecal injections of 10,000 to 20,000 units were followed by fluid levels of from 5.0 to 19.0 units

per cubic centimeter twelve hours later and by levels of 0 to 2.45 units (average 0.69) twenty-four hours later. The lumbar route of injection is the simplest and is usually adequate. The drug in two cases was observed to pass freely from the spinal into the interventricular fluid. In an earlier case,[12] however, this passage failed to occur. Also, we have clinical reasons to believe that in some cases cisternal injections are more effective than the lumbar.[13]

In one early peritonitis, fluid assay revealed .039 units one hour after 40,000 units penicillin were injected intramuscularly.

ANALYSIS OF CLINICAL MATERIAL

The analysis of clinical material covers 255 conditions in 220 patients for which penicillin treatment was administered. The cases to follow have been classified as disease entities and surgical or medical problems rather than according to the organisms cultured.

Soft Tissue Infections.—

Carbuncles and furuncles (13 cases): The morbidity of carbuncles and furuncles has been markedly reduced from that to be expected with sulfonamide therapy. The number of days until the lesion was nearly healed averaged 9.25 days for the carbuncles and 10 days for the furuncles. That external application of penicillin is of no benefit in these infections is well illustrated by the case of a young aviator treated for furunculosis of the scalp by local applications of penicillin in tragacanth jelly (250 units per cubic centimeter). The lesions soon reached such alarming proportions that intramuscular injections of 15,000 units every three hours were started. Within forty-eight hours the furuncles had melted down to tiny crusted papules.

In a number of instances it was observed that the carbuncle or furuncle, especially when the patient was given a heavy initial dose of penicillin, within twenty-four to thirty-six hours became more angry, swollen, and painful, the patient often feeling more toxic than before. There would then, within the next few hours, follow swift regression of the lesion, usually with suppuration and relief of pain. We have interpreted this Herxheimer-like reaction as possibly a clinical indication of a definite lysis of the staphylococcus and liberation of its endotoxin.

In no instance was it necessary to incise and drain a penicillin treated carbuncle or furuncle. Rapid liquefaction and spontaneous drainage invariably occurred. Our only interference was to pluck out the necrotic slough which formed with unusual rapidity.

Cellulitis and abscess of soft tissue in general: In a group of twenty cases our clinical appraisal in comparison with what might have been expected with sulfonamide drugs was as follows:

Result equal to sulfonamides	5
Result superior to sulfonamides	10
Exceptionally good result	4
Failure	1

Five times in this series penicillin overcame an infection after sulfonamides proved ineffectual. The one failure in the group was in a case of peculiar multiple burrowing sinuses of the arms and legs which baffled all diagnosis and treatment.

Cases 1, 2, and 3 from this group were of particular interest.

CASE 1.—Chronic ulcers of the toes in a patient with thromboangiitis obliterans, that had for months resisted all other treatments, healed in two weeks under penicillin.

CASE 2.—A very severe cellulitis with abscess formation of the left cheek (see Fig. 2) which had grown progressively worse on adequate sulfadiazine therapy rapidly resolved under local treatment, consisting of aspirating the pus (containing alpha streptococci and *Staphylococcus albus*) and injecting locally, through the same needle, 25,000 units of penicillin on six occasions.

A. *B.*

Fig. 2.—Patient (Case 2) with severe cellulitis of face, not of salivary or osteomyelitic origin; temperature ranging from 101 to 102° F. *A*, At start of local penicillin therapy; *B*, on fourth day of local penicillin therapy.

CASE 3.—A patient with diffuse subcutaneous abscesses of several fingers harbored highly penicillin-susceptible staphylococci. In spite of penicillin dosages increased to 40,000 units intramuscularly every three hours, no response was obtained until multiple incisions were performed releasing pus under tension. Once drainage was established, the infection quickly subsided. This illustrates the impotence of penicillin against infection involving pus in closed spaces, however small.

Infected operative wounds: Seven cases of infected operative wounds include three inguinal herniorrhaphy wounds, a bilateral radical upper neck dissection, a laparotomy wound, a large secondarily closed wound of the hip, and

a primarily closed pilonidal sinus wound. With the exception of the pilonidal excision wound, all healed solidly and essentially per primam within an eighteen-day average, after one or two skin stitches had been removed to allow escape of pus. Staphylococci were isolated from four of these and hemolytic streptococci from the other two.

The pilonidal wound infected with staphylococci and a highly resistant fecal streptococcus proceeded to complete breakdown while receiving 120,000 units of penicillin a day.

Threatened and established cavernous sinus thrombosis: Six cases are summarized in Table I. It will be observed that four cases, although not full blown,

TABLE I. PENICILLIN IN THREATENED AND ESTABLISHED CAVERNOUS SINUS THROMBOSIS

CASE NO.	AGE	DIAGNOSIS	BACTERIOLOGY	PENICILLIN	RESULTS
1	24	Threatened cavernous sinus thrombosis, left, following nasal operation	Beta hem. Str. coagulase positive; hem. Staph. aureus	380,000 U. in 3 days	Worse after 48 hr. on sulfa; rapid subsidence under penicillin
2	26	Threatened cavernous sinus thrombosis from furuncle, left nostril	Blood stream and wound; hem. Staph. aureus	4,960,000 U. in 22 days	Worse after 36 hr. on sulfa; pulmonary infarcts, subsided without residuals
3	26	Threatened cavernous sinus thrombosis from frontal sinusitis	Hem. Staph. aureus; Beta hem. Str.	1,965,000 U. in 10 days	Orbital cellulitis subsided by 4th day and frontal sinusitis by 9th day
4	20	Threatened cavernous sinus thrombosis from ethmoiditis	Ethmoid sinus; Pneumococcus type 10	2,225,000 U. in 9 days	Orbital cellulitis subsided by 4th day and apparently was cured by 10th day
5	20	Cavernous sinus thrombosis, left; fungus infection of skin	Blood culture; negative nostril; hem. Staph. aureus coagulase positive	4,890,000 U. in 16 days	Sinus thrombosis cured but died from uncontrollable fungus skin ulcerations
6	19	Cavernous sinus thrombosis and multiple brain abscesses	Hem. Staph. aureus; anaerobic Str.	615,000 U. in 1 day	Moribund with sepsis both of brain and of sinus; died

were called "threatened cavernous sinus thrombosis" by the ophthalmologic consultants because of early papilledema, ophthalmoplegia, or both, along with the marked orbital cellulitis and conjunctival edema. One patient (Case 2), shown in Fig. 3, had a positive staphylococcus blood culture and several pulmonary infarcts. Patients (Cases 5 and 6) with established cavernous sinus thrombosis died. One (Case 6) also had multiple brain abscesses and was moribund on entry. Another (Case 5) at the outset received 90,000 units of penicillin by intravenous drip. His condition growing rapidly worse, the dose was increased to 360,000 units daily and heparin and dicoumarin were given. Thereafter the major infection regressed satisfactorily. Then, after surviving the cavernous sinus thrombosis, he developed multiple rapidly necrotizing ulcerations of the face, groin, and thighs to which he finally succumbed. Repeated cultures, aerobic, anaerobic, and for fungi, revealed only *Staph. albus* and a fungus "rarely pathogenic to man," Gomphaneria Petrosoi.

Penicillin as Adjunct to Surgical Procedures.—

In extensive clean or in contaminated operative cases: The sixteen cases include the following.

Nine patients with radical block dissections of the neck received 160,000 to 200,000 units daily with average total of 1,700,000 units. One hundred twenty thousand units daily would probably have sufficed. All healed per primam; none developed more than slight amount of fluid beneath the skin flaps; one developed marked facial edema and two moderate edema; one developed temporary minimal wound infection. A nontreated neck dissection during this period developed a severe streptococcal wound infection.

A. *B.*

Fig. 3.—Patient (Case 2, Table I) with threatened cavernous sinus thrombosis, staphylococcemia, and multiple pulmonary infarcts, secondary to furuncle, left nostril. *A*, Day following commencement of penicillin; *B*, sixth day after commencement of penicillin.

One patient having developed marked facial edema following bilateral upper block dissection of the neck and another with postoperative hematoma and drainage following excision of a branchial cleft cyst, both subsided nicely without infection on the drug.

The wounds in a baby with a harelip operation and an adult who underwent a difficult excision of a recurrent thyroglossal fistula both healed per primam.

Three patients with extensive shell fragment wounds received prophylactic penicillin: one with an avulsion wound of the buttock and one with laceration of the liver healed without infection. The third with a large tear in the rectum communicating with a shattered upper femur developed a blood stream

infection with hemolytic streptococcus, *Str. fecalis,* and *Staph. albus* and died in spite of one-half million units of penicillin a day. We have so far received from overseas no survivors of a rectal injury communicating with a compound fracture of the femur.

Excision and closure of granulating wounds: Of granulating wounds there were twenty-four wounds in sixteen soldiers with an over-all success in seventeen and failure in seven. These wounds almost universally cultured *Staph. aureus* and *Staph. albus,* a few also contained *Str. faecalis, diphtheroids,* and *B. coli.* From Table II it can be seen that the largest number of failures occurred among

TABLE II. PENICILLIN IN EXCISION AND CLOSURE OF GRANULATING WOUNDS

DESCRIPTION	PENICILLIN DOSAGE	RESULTS
Ten decubiti in 3 paraplegias	200,000 U. daily	5 successful, 5 failed
One decubitus in a paraplegia	Local instillation through fine tube	Successful
Four amputation stumps	120,000 to 240,000 U. daily	3 drained thin staphylococcus-containing fluid but healed soundly; 1 failed
One reamputation 2 inches above infected amputation through knee	200,000 U. daily	Healed soundly after draining staphylococcal fluid
Eight granulating abscesses or infected sinuses	120,000 to 240,000 U. daily	7 healed per primam though one drained a scant amount; 1 failure in a small sinus of thigh

the decubiti, that the closed amputation stumps usually healed after a period of seropurulent drainage culturing staphylococci, and that wounds and sinuses (Figs. 4 and 5) almost always healed nicely.

It should also be mentioned that during the present study a decubitus receiving no other treatment than local boric compresses was excised and closed with per primam healing.

From the patient shown in Fig. 4 with a laminectomy wound, hemolytic *Staph. aureus,* sensitive to 2.85 Oxford units, was cultured; yet the wound cleaned up remarkably well allowing secondary closure twenty-nine days after the original laminectomy and while still harboring staphylococci. The granulating wound of the patient shown in Fig. 5 still cultured staphylococci at time of closure, yet per primam healing ensued. Such cases demonstrate a powerful factor supplied by the host which, in conjunction with penicillin, achieves clinical results unsuspected from cultures and in vitro sensitivity tests.

Pilonidal sinus excision and primary closure: Under a daily intramuscular dosage of 200,000 units of penicillin, eleven recently infected pilonidal sinuses in ten patients were excised and primarily closed using fine silk or cotton technique. Six broke down and five healed per primam. Staphylococci were present in all the failures and in two of the successful closures. This is a poor percentage for penicillin compared to the good results obtained in excision and closure of soft tissue wounds elsewhere with similar flora. It would seem to attest to the local peculiarity of anatomy of the lesion as well as to the local bacteriology. It was our clinical impression that local penicillin with or without the parenteral administration somewhat facilitated healing by granulation even when primary closure had proved unsuccessful.

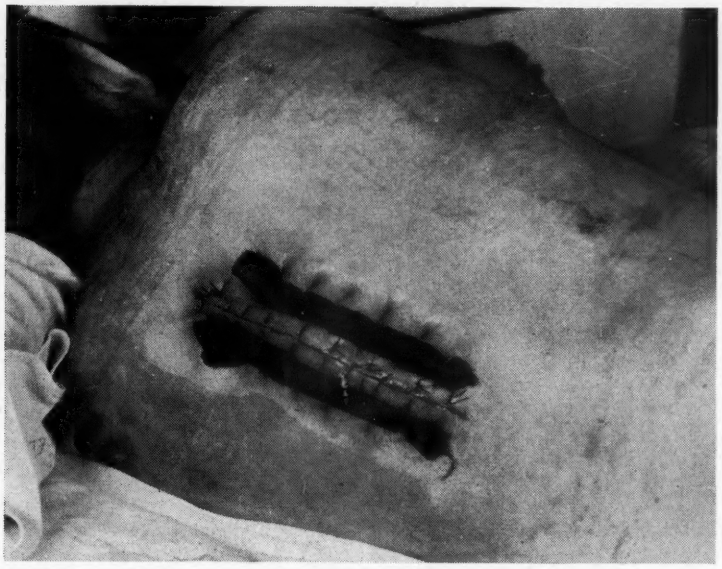
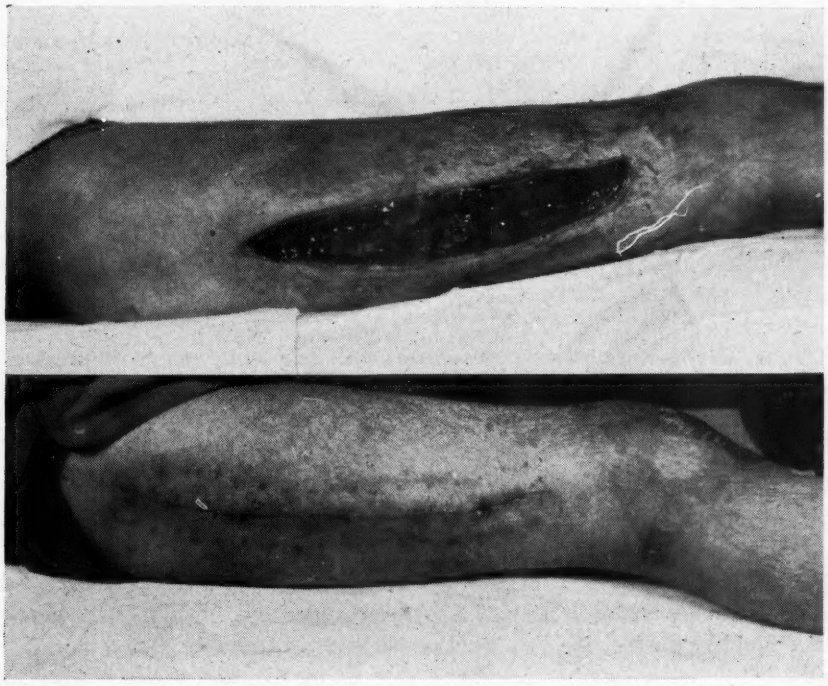


Fig. 4.—Epidural abscess necessitating surgical excision of laminae, fifth to eleventh dorsal vertebrae inclusive; secondarily closed twenty-nine days postlaminectomy. Photograph taken three days after secondary closure; healed by first intention.

A.



B.

Fig. 5.—Subfascial abscess of right thigh of life-endangering severity, complicating operation on knee joint and not responding to sulfonamide therapy. *A*, Twenty-two days following radical incision and drainage, and nineteen days after start of penicillin; *B*, eighteen days after secondary wound closure, done twenty-four days after incision and drainage.

Skin grafting: It is interesting that the only 100 per cent take (Case 7, Table III) was on a sacral decubitus to which only boric compresses were applied. In a bilateral granulating burn of the legs (Case 4, Table III) although

TABLE III. PENICILLIN IN SKIN GRAFTING

PATIENT NO.	AREA GRAFTED	GRAFT	TREATMENT	RESULTING "TAKE" (PER CENT)
1	Granulating burn, hand	Thiersch	Penicillin jelly	70
1	Granulating burn, temple	Thiersch	Penicillin jelly	95
1	Granulating burn, leg	Thiersch	Penicillin jelly	95
2	Granulating burn, leg	Dermatome	Penicillin jelly	50
3	Granulating burn, leg	Dermatome	Penicillin jelly 120,000 U. a day parenteral	45
4	Granulating burn, leg	Dermatome	Penicillin compress	90
4	Granulating burn, leg	Dermatome	Boric compress (no penicillin)	90
5	Granulating wound, leg	Dermatome	Penicillin jelly 200,000 U. a day parenteral	75
6	Granulating wound, back	Dermatome	Penicillin compress	0
7	Sacral decubitus	Dermatome	Boric compress (no penicillin)	100
8	Sacral decubitus	Dermatome	Penicillin compress	0
8	Sacral decubitus	Dermatome	Penicillin 200,000 U. a day parenteral	0
9	Sacral decubitus	Dermatome	Penicillin 200,000 U. a day	80

the degree of take was equal on the penicillin and control side, the latter showed the smoother, better graft. The graft on the decubitus (Case 8, Table III) failed completely, both when local and when parenteral penicillin was used.

Two recently observed patients not in this series showed little benefit from penicillin.

CASE 1.—A soldier with granulating burns of chest and thigh received a dermatome graft to the thigh while on 200,000 units penicillin a day, with 70 per cent take. A few days later, while receiving only an occasional local dressing of penicillin jelly, the lesion of the chest was grafted with 60 per cent take.

CASE 2.—An officer with a large granulating shell fragment wound of the thigh received first a dermatome graft while getting no medication. The graft was 40 per cent successful. A few days later, while receiving penicillin both locally in saline compresses and parenterally in daily doses of 160,000 units, his wound was regrafted with complete failure.

From these few cases it would appear that in such wounds where infection is at a minimum, and where much of the flora is resistant to penicillin, metabolic factors and technical details play the dominant role and that the drug adds little to the chance of success of the graft. Hirshfeld and co-workers,[14] however, were enthusiastic over the benefit of parenteral penicillin in a series of nineteen skin grafts.

To conclude, penicillin is indisputably of paramount value in the surgery of contaminated wounds. This is being eloquently proved by our forward surgeons[15, 16] in the theaters of war. It is indicated, but less convincingly so,

in very long operations where asepsis cannot be made absolutely ideal, and in secondary wound closure. In skin grafting and primary closure of pilonidal sinus excision wounds its value is still to be proved.

Penicillin in Bone and Joint Infections.—

Osteomyelitis and septic compound fractures: Our experience consists of eleven cases of staphylococcal hematogenous osteomyelitis and eighteen cases of secondary osteomyelitis and septic compound fractures, also predominantly staphylococcal, as summarized in Tables IV and V, respectively. These few

TABLE IV. PENICILLIN IN HEMATOGENOUS OSTEOMYELITIS

CASE NO.	AGE	DESCRIPTION	TREATMENT	RESULTS
1	4 mo.	Osteo.* of humerus with staphylococcemia	Parent.† 443,000 U. in 30 days; drainage of soft tissue abscess	Inactive by 56th day; involucrum formed
2	11 yr.	Osteo. of upper tibia	Parent. 1,640,000 U. in 10 days + local; drainage and drilling of bone	Sinus persists after 247 days; sequestration
3	37 yr.	Flare-up of old osteo., lower femur	Parent. 4,359,000 U. in 36 days + local; wide drainage and curettement of bone	Healed with excellent function 47th day
4	19 yr.	Osteo. of tarsals of foot	Parent. 3,200,000 U. in 31 days; incision and drainage of soft tissues	Healed without sequestration 63rd day
5	22 yr.	Osteo. of upper femur and arthritis, hip joint	Parent. 9,610,000 U. in 52 days + one 10,000 U. local injection; no surgery	Healed with normal joint motion 90th day
6	22 yr.	Osteo. of upper femur and arthritis, hip joint	Parent. 10,145,000 U. in 33 days; late in disease abscess of hip drained	Joint destroyed; still draining after 1½ yr.
7	30 yr.	Old Brodie's abscess of femur with sinus	Parent. 2,310,000 U. in 19 days; extraction of small sequestrum and curettement	Healed 17 days after removal of sequestrum
8	25 yr.	Osteo. of radius with sequestration	Parent. 8,250,000 U. in 55 days; saucerization and primary wound closure	Wound healed per primam
8	25 yr.	Osteo. of ilium (same patient as above)	Parent. 8,250,000 U. in 55 days; sequestrectomy	Wound healed by 43rd day
9	35 yr.	Osteo. of ilium and sacroiliac joint	Parent. 10,350,000 U. in 79 days after local penicillin failed; sequestrectomy	Wound healed by 150th day
10	29 yr.	Osteo. of ilium and sacroiliac joint	Parent. 11,300,000 U. in 56 days + local, sequestrectomy	Wound healed by 89th day

*Osteo., osteomyelitis.
†Parent., parenteral.

cases raise some interesting questions. The characteristically rapid relief of pain in these cases was well demonstrated in patients (Case 5, Table IV, and Cases 4 and 6, Table V) who were relieved of their suffering in twenty-four, forty-eight, and nine hours, respectively. The first two of these patients had been unimproved by adequate sulfadiazine therapy.

In Cases 2 and 7, Table IV, and Cases 2 and 3, Table V, penicillin showed no superiority to what might be expected of the sulfonamides. In all other instances it showed definite superiority to the results obtained or to those

TABLE V. PENICILLIN IN SECONDARY OSTEOMYELITIS AND SEPTIC COMPOUND FRACTURES

CASE NO.	AGE (YR.)	DESCRIPTION	TREATMENT	RESULT
1	25	Infected compound fracture of upper femur	Parent.* 9,660,000 U. in 86 days + local; wound explored 3 times	Healing 94th day after removal of fragments
2	30	Fracture, neck of femur, with infected bone graft	Parent. 6,170,000 U. in 56 days + local; incised and drained once	Wound continued to drain
3	23	Infected compound fracture of upper femur	Parent. 2,520,000 U. in 22 days; exploration and drainage of wound	Drainage continued; leg amputated
4	26	Infected amputation stump, leg; periostitis, tibia	Parent. 4,050,000 U. in 25 days; later reamputated 2 in. higher	Infection controlled; slight drainage persisted
5	28	Infected amputation stump, leg; periostitis, tibia	Parent. 6,135,000 U. in 31 days; no surgery	Healed in 40 days in spite of poor blood supply
6	21	Infected amputation stump, leg, with 4 cm. bare tibia	Parent. 6,895,000 U. in 34 days; excision ¼ in. of tip of tibia	Nearly healed 34th day when transferred
7	23	Infected, severely lacerated compound fracture of fibula†	Parent. 7,725,000 U. in 55 days + local; no surgery	Soft tissue wound healed 67th day
8	33	Low-grade anaerobic infection bone graft, tibia‡	Parent. 6,430,000 U. in 20 days; no surgery	Slow subsidence after sulfonamide therapy had failed
9	29	Septic compound fracture of humerus and glenoid process	Parent. 3,675,000 U. in 36 days + local; excision of head and neck of humerus	Smooth P.O. course; healed 36th day
10	27	Infected inlay bone graft for nonunion, ulna	Parent. 2,611,000 U. in 14 days; no surgery	Graft saved; wound healed by 14th day
11	30	Osteo.,§ iliac crest, from gunshot wound	Parent. 6,697,000 U. in 46 days + local; sequestrectomy	Wound healing complete 46th day
12	32	Osteo., head 2nd metatarsal from nail puncture	Parent. 3,720,000 U. in 24 days; no surgery required	Infection resolved; function restored
13	22	Osteo., postoperative, lamina lumbar 4	Parent. 4,775,000 U. in 36 days; early sequestrectomy	Sound healing 41st day
14	25	Osteo., postoperative, laminae lumbar 4 and 5	Parent. 350,000 U. in 15 days (inadequate); no sequestrectomy	Prolonged drainage; healing about 140th day
15	20	Osteo., skull secondary to frontal sinusitis; brain abscess	Parent. 15,730,500 U. in 99 days + local; sequestrectomy later	Wound healed 37th day (14th day P.O.)
16	44	Osteo., left mandible, early, and severe cellulitis of face	Parent. 5,270,000 U. in 50 days; drainage of submandibular abscess	Rapid control of cellulitis; early osteo. aborted
17	39	Osteo. of maxilla with multiple small sequestra	Parent. 2,250,000 U. in 18 days; removal of several small sequestra	Gums healed 37th day
18	25	Osteo. of ascending ramus of mandible	Parent. 4,625,000 U. in 44 days; intraoral curettement of ramus	Steady progress to complete destruction, ramus

*Parent., parenteral.

†Culture included *Cl. welchii* without clinical gas gangrene.

‡Organisms isolated at first (but not at second) aspiration: *Cl. sporogenes* and *Cl. aerofetidum.*

§Osteo., osteomyelitis.

which might have been expected to the sulfonamide drugs. In Cases 4 and 5, Table IV, and Cases 5, 10, 12 and 15, Table V, penicillin proved brilliantly successful after sulfadiazine had failed.

The following cases demonstrate what may be accomplished by penicillin.

CASE 5 (Table IV).—A 22-year-old white sergeant with early osteomyelitis of the left upper femur and septic arthritis of the hip joint, at first undiagnosed, was treated from September 26 to October 12, 1943, on oral sulfadiazine. Upon arrival at Walter Reed General Hospital his temperature was spiking to 103° and 104° F.; he was acutely ill and in great pain, holding his left thigh rigidly flexed and internally rotated. Seven cubic centimeters of thick pus culturing hemolytic *Staph. albus*, coagulase positive and sensitive to 0.4 units penicillin, were aspirated and 10,000 units penicillin injected in 10 c.c. normal saline solution. At the same time intramuscular injections of 30,000 units every three hours and dicoumarin therapy were instituted, traction being applied to the lower extremity over Buck's extension. Within twenty-four hours there was marked relief of pain and progressive improvement followed. Penicillin was discontinued Dec. 3, 1943, and by Jan. 12, 1944, the soldier was allowed up and around on crutches. When last seen, March 3, 1944, three months after cessation of penicillin, he was free of symptoms and had perfect range of hip motion. Roentgenograms, which had shown progressive bone destruction of the upper femur up to mid-November, 1943, by this time showed considerable healing and new bone formation.

CASE 12 (Table V).—A 32-year-old Norwegian commando instructor stepped on a nail June 2, 1943, developing low-grade osteomyelitis of the left second metatarsal as proved by x-ray picture. There was swelling, pain, and low spiking fever failing to respond to sixteen days of intensive sulfadiazine with blood levels 12 to 14 mg. per cent. His foot was immobilized in plaster and he received penicillin therapy as shown in Table V. When last seen Aug. 16, 1943, he was taking ten-mile hikes and x-ray views showed arrest of the destructive bone process without evidence of sequestration.

CASES 6 AND 10 (Table V).—The first patient, with a badly infected (beta hemolytic streptococcus and *Staph. aureus*) lower leg amputation stump, the second with an infected inlay bone graft for nonunion of the ulna, culturing hemolytic *Staph. aureus*, presented the serious problem of rough denuded bone and badly infected soft tissues. In addition, in Case 10 it was feared that the bone graft with its metal fixation screws would fail. Under penicillin therapy, the patient healed completely in fourteen days and the graft was saved. In Case 6, after one-quarter of an inch of the tibial tip was excised, granulation tissue rapidly closed over the remaining bare bone. The stump was practically healed when the patient was transferred to another hospital thirty-four days after the start of treatment.

That penicillin can prevent sequestration in acute osteomyelitis and obviate radical surgical intervention is demonstrated by Cases 4 and 5, Table IV, and Cases 12 and 16, Table V. Drainage of soft tissue abscess was necessary in Case 4, Table IV, and Case 16, Table V. In the remaining seven patients (Cases 1, 2, 6, 8, and 10, Table IV and Cases 15 and 17, Table V) with acute osteomyelitis, sequestration occurred and surgical intervention of varying magnitudes was necessary. Thus (Case 2, Table IV), a young girl, receiving early and vigorous treatment (200,000 units daily) proceeded to sequestration and sinus formation. Possibly a much larger initial dosage, longer continued therapy, and repeated aspiration of pus instead of the more destructive surgery might have succeeded better.

The outcome in any of these cases was unpredictable at the outset because it depended upon the fate of the blood supply to the infected bone. We have lately become impressed with the unexpected success achieved by greatly in-

creased dosages, and wonder if early osteomyelitis might not be more often arrested if huge amounts of penicillin were given initially in the attempt to get an effective quantity of the drug across the barrier of thrombosing arterioles and capillaries where a lower blood level would fail. Concomitant anticoagulant therapy has not been satisfactorily investigated. What share the dicoumarin had in the remarkable result obtained in Case 5, Table IV, we cannot say.

Probably the least satisfactory response of all bone suppurations is the septic compound fracture of the femur. There were two failures among the three wounds of this type (Cases 1, 2, and 3, Table V). The explanation may possibly lie in the large muscle mass surrounding the bone capable of hiding sequestra and rendering drainage difficult. Thus, in Case 1 drainage persisted a long time and not until the third exploration was a pocket discovered, harboring numerous small necrotic bone fragments. Healing occurred soon thereafter.

As to osteomyelitis of the skull and pelvis (see Cases 8, 9, and 10, Table IV, and Cases 11 and 15, Table V), in no instance was healing achieved without surgical removal of necrotic bone. However, a single sequestrectomy together with penicillin was followed by healing in all cases. It is noteworthy that in Case 9, Table IV, in spite of twenty aspirations of pus with local injection each time of 10,000 to 25,000 units penicillin along with parenteral therapy, the process continued to advance until radical surgery was resorted to.

Our experience with primary closure of soft tissues following sequestrectomy in subacute and chronic osteomyelitis is limited to a single but satisfactory instance, Case 8, Table IV. However, wherever the soft tissues permit of closure without tension and dead space, this would appear to be a feasible procedure.

In chronic osteomyelitis we have several times observed, as have others,[17, 18] that even though the drainage may become temporarily sterile under penicillin, at operation staphylococci may still be cultured from the depths of the involved bone and sclerotic tissues where they have evidently been sealed away beyond the reach of the blood borne or locally instilled agent. These mechanical and vascular factors explain the difficulty of treating chronic skeletal infections and also their unpredictable recurrences.

Septic arthritis: Of our small group of five cases of septic arthritis only one patient had complete recovery and one partial. These two (Cases 1 and 5, to be discussed) received penicillin locally whereas the other three did not. Although about 50 per cent of the circulating drug crosses the synovial membrane[7] it is well to supplement parenteral with local injections of penicillin. Brief descriptions of the cases follow.

(1) CASE 5 (Table IV, previously described in detail).—A patient with osteomyelitis of the upper left femur and septic arthritis of the hip joint had complete restoration of hip motion following a single local injection of 10,000 units of penicillin and intramuscular injections totaling 9,650,000 units.

(2) CASE 6 (Table IV).—A patient with a lesion closely similar to that of the patient in Case 5 received 10,145,000 units intramuscularly and none locally. Complete destruction of the hip joint and a persistently draining sinus resulted.

(3) A postoperative staphylococcal suppuration of the knee joint following an open reduction of a fractured tibial condyle was widely drained. The patient received 4,075,000 units parenterally but none locally. The severe general sepsis was easily overcome but the knee ankylosed.

(4) A patient with mixed streptococcal and staphylococcal arthritis of the proximal joint, index finger, following a laceration that entered the joint, received 3,800,000 units parenteral penicillin but ended with amputation of the finger.

(5) A patient with staphylococcal suppuration of the fifth metacarpophalangeal joint, likewise of traumatic origin, was treated by local instillations through a ureteral catheter as well as by 2,400,000 units of parenteral penicillin. Healing followed but with a rather stiff, swollen, somewhat painful joint.

Penicillin in the Treatment of Burns.—Our experience with penicillin in burns consists in the seven cases shown in Table VI and in a few later cases not included in this report.

TABLE VI. PENICILLIN IN THE TREATMENT OF BURNS

CASE NO.	AGE (YR.)	DESCRIPTION OF BURN (LOCATION, PER CENT BODY SURFACE INVOLVED, DEPTH, DURATION)	PENICILLIN TREATMENT	RESULTS
1	28	Hand; about ½%; 2nd degree; 8 hr. old	Local in aquafor	Healed 10th day; no clinical infection
2	22	Face, head, hands, legs; total 15%; 2nd & 3rd degree; 12 days old	Local in tragacanth jelly	Healed, with grafting on 46th day
3	29	Thighs, legs; total 7%; chiefly 3rd degree; 120 days old	Local in tragacanth jelly	Healed with grafting on 46th day
4	55	Rt. arm, thigh, leg and perineum; total 13%; 2nd and 3rd degree; 36 hr. old	Parent.* 5,424,000 U. in 44 days; local in aquafor	Probably saved life; nearly healed 70th day
5	25	Neck, shoulder, arm; total 5%; 3rd degree, infected; 160 days old	Local in tragacanth jelly	Checked infection when sulfonamide failed
6	26	Face, head, forearms; total 22%; 2nd and 3rd degree; 36 hours old	Parent. 2,050,000 U. in 11 days; no local	Died 11th day; cause undetermined
7	23	Thighs and legs; total 18%; 3rd degree; 60 days old	Parent. 3,480,000 U. in 28 days; local in aquafor	Died 28th day; cause undetermined

*Parent., parenteral.

In the fresh extensive burn such as Case 4, Table VI, parenteral penicillin as a prophylaxis against infection should supplant the sulfonamides since it is more potent against streptococci and staphylococci and has none of their untoward side effects. The aforementioned patient, extremely obese, hypertensive, and possessing an enormous ventral hernia had a relatively smooth course, never developing sepsis in the deep second degree burns.

Penicillin applied locally in a water-soluble base (200 to 250 units per cubic centimeter) is a very satisfactory dressing for minor burns such as were found in Case 1, Table VI. We have also used the local application for the sloughing and granulating stage of third degree burns prior to skin grafting as in Cases 2 and 3, Table VI. When these lesions are relatively clean and harbor only the inevitable staphylococci of low pathogenicity and high resist-

ance to penicillin and other lesser flora, penicillin, local or parenteral, shows little if any superiority over any of the several accepted local dressings. However, in intercurrent sepsis as in the patient (Case 5, Table VI) who developed a mixed streptococcal and staphylococcal infection, the new drug given locally or parenterally, or both, demonstrates its superiority.

The cause of death in Cases 6 and 7, Table VI, was not explained but seemed to be unrelated to local wound sepsis.

Penicillin in Central Nervous System Infections.—In a separate publication[13] the views of this Hospital upon the subject of penicillin in central nervous system infections have been set down in connection with a slightly different series of patients. Our total dosages, routes of administration, and results are outlined in Table VII.

The penicillin cure of the patient (Case 2, Table VII) with a brain abscess secondary to lung abscess is almost unique in medical history. King[19] in 1936 gleaned reports of several successfully treated metastatic brain abscesses from the literature, two or three being secondary to pulmonary suppuration.

Penicillin has proved to be outstandingly effective against brain abscess. It rapidly resolves the cerebritis accompanying the incipient lesion that heretofore killed before there was enough localized pus to be drained surgically. It is important to remember that this drainage, just as soon as penicillin has brought about localization, is an indispensable step in the management of the disease.

Case 1, Table VII, brought out a second interesting feature. Once the pyogenic membrane had formed, the parenterally administered drug had no effect upon the frontal lobe abscess. Pus loaded with anaerobic streptococci and showing no penicillin activity continued to form while 120,000 units a day were given intramuscularly. After several local injections of 50,000 to 75,000 units directly into the abscess, it was sterilized and a few days later it was successfully enucleated. At this time contents and wall were sterile.

A postoperative osteomyelitis (Case 7, Table VII) of the fourth lumbar lamina, treated by early excision of the involved portion of the lamina together with vigorous penicillin dosage, was healed by the forty-first day, whereas the patient (Case 8) with a closely similar condition, but receiving no surgery and too little drug (treated in the early days of penicillin), required 140 days for healing!

Penicillin in Surgical Infections of the Chest.—The twenty-five cases in Table VIII are divided into four groups: empyema, lung abscess without lobectomy, lung abscess with lobectomy, and bronchiectasis with lobectomy. These cases were studied in close conjunction with Lieutenant Colonel B. B. Blades of the Thoracic Surgery Section.

Empyema: Most of the cases are included in a series of twenty-four penicillin-treated empyemas separately published[20] but with the same conclusions as here expressed. Of the present group, although most of the patients were given a fair trial of parenteral and local injections and repeated aspirations,

TABLE VII. PENICILLIN IN CENTRAL NERVOUS SYSTEM SEPSIS

CASE NO.	AGE (YR.)	DIAGNOSIS	CULTURE	TREATMENT	RESULT
1	20	Pansinusitis, frontal osteomyelitis, frontal lobe abscess	Staph. aureus; anaerobic hem. Str.	Parent.* 15,355,000 U. in 99 days + local 375,000 U.; surgery to skull and abscess	Complete recovery 120th day; returned to duty
2	23	Cerebellar abscess secondary to lung abscess	Nonhem. Str.	Parent. 14,360,000 U. in 53 days, local 75,000 U.; drainage of abscess	Recovery 53rd day; lung abscess also quiescent
3	27	Postoperative temporal lobe abscess and meningitis	Abscess and spinal fluid; Staph. aureus	Parent. 3,287,000 U. in 14 days, local 107,000 U.; drainage of abscess	Recovered and discharged home 32nd day
4	22	Frontal lobe abscess from fracture of cribriform plate	Staph. aureus; non-hem. Str.	Parent. 5,295,000 U. in 36 days, local 25,000 U.; drainage of abscess	Developed brain fungus; recovery delayed to 200th day
5	23	Large epidural abscess, etiology obscure	Hem. Staph. aureus sensitive to 4.0 U.	Parent. 7,650,000 U. in 36 days + local; laminectomy, later secondary closure	Ambulatory 41st day; returned to duty 165th day
6	38	Postoperative epidural abscess covering entire lumbar cord	Beta hem. Str. sensitive to .0025 U.	Parent. 2,060,000 U. in 13 days + local; no surgery	Decompression obviated; healed 20th day; duty
7	22	P.O. osteomyelitis 4th lumbar lamina and epidural abscess	Hem. Staph. aureus sensitive to .0078 U.	Parent. 4,775,000 U. in 36 days; sequestrectomy at outset	Healing complete 41st day; returned to duty 125th day
8	25	P.O. osteomyelitis 4th lumbar lamina and epidural abscess	Staph. aureus; Staph. albus	Parent. 45,000 U. in 15 days; no local, no sequestrectomy	Final healing not till 140th day; returned to duty 172nd day
9	22	Meningitis from basilar skull fracture into frontal sinus	Staph. aureus coagulase positive	Intrathecal and later intraventricular; total 112,500 U., no parenteral	Sulfonamide failure; intraventricular better than intrathecal; survived
10	47	Late, neglected meningococcus meningitis	Probable meningococcus	Parent. 2,046,000 U. in 9 days; local 120,000 U., intrathecal and cysternal	Never completely conscious; died 11th day
11	5	Purulent meningitis	Organism unidentified	Parent. 1,585,000 U. in 40 days; local 197,000 U.	Recovered
12	22	Acute mastoiditis, septicemia, meningitis	Beta hem. Str. throughout	Parent. 625,000 U. in 3 days, no local; mastoidectomy night of entry	Died 2nd day of pulmonary edema in spite of sterilized blood and spinal fluid

*Parent., parenteral.

TABLE VIII. PENICILLIN IN

CASE NO.	AGE (YR.)	DIAGNOSIS	BACTERIOLOGIST
1	27	Empyema formed while getting penicillin for pneumonia	Pneumococcus Type I; susceptible to .0025 U.
2	21	Empyema, left, coincident with pneumonia	Staph. aureus, susceptible to .35 U.
3	18	Empyema, left, complicating lobar pneumonia, left	Hem. Staph. aureus, susceptible to .04 U.
4	35	Empyema, left complicating pneumonia	Beta hem. Str.
5	30	Empyema, right, complicating pneumonia	Beta hem. Str.
6	36	Empyema, left, complicating pneumonia	Beta hem. Str.
7	18	Empyema, right, complicating pneumonia	Beta hem. Str.
8	26	Empyema, left, complicating atypical pneumonia	Hem. Staph. aureus
9	37	Empyema, left, following lobar pneumonia	Pneumococcus Type V; susceptible to .02 U.
10	20	Bronchiectasis, left lower lobe, with secondary pyopneumothorax	Nonhem. Str.; Staph. albus and mixture
11	29	Lung abscess, left upper lobe, 4 weeks' duration	Mixed flora; no predominant organisms
12	40	Lung abscess, left upper lobe, 9 weeks' duration	Predominant, alpha Str. mitis
13	25	Acute lung abscess, right upper followed by same in right lower	Predominant, alpha Str. salivarius
14	43	Multiple lung abscesses, right upper lobe, 4 mo. duration	Alpha Str. of 2 varieties
15	35	Lung abscess, right upper, with much pneumonitis, 5½ mo.	Chiefly alpha Str.; few Beta Str.
16	23	Multiple lung abscesses, left upper, 3 mo. duration; secondary brain abscess	Alpha hem. Str. salivarius
17	24	Lung abscess, left lower lobe, 4 mo. duration	Alpha Str.; at times Beta Str.
18	27	Lung abscess, multiple, right upper lobe, 6 mo. duration	Alpha and Beta Str.; at times Staph.
19	30	Infected cyst left lower lobe simulating abscess, 4 mo.	Alpha Str.; non-hem. Str.
20	24	Putrid empyema, P.O., from lobectomy for chronic lung abscess	Str. faecalis; diphtheroids
21	22	Lung abscess, right upper, 8 mo. duration	Abscess; Beta hem. Str., empyema, no growth
19	30	Putrid empyema, early, following lobectomy (same as Case 17)	Hem. Staph. albus; hem. influenzae
18	27	Lung abscess, multiple, right upper lobe, 12 mo. duration	Alpha hem. Str. and a mixture
22	40	Bronchiectasis, left lower lobe with large cyst formation, 9 mo.	Alpha hem. Str.
10	20	Case 10 above, cystic bronchiectasis, after healing of empyema	None obtained

Note: Three patients in this group (Cases 10, 18, and 19) appear twice, since they each represent two distinct applications of penicillin therapy with an interval between.

*Parent., parenteral.

SURGICAL CHEST CONDITIONS

TREATMENT	RESULTS
Parent.* 1,650,000 U. in 14 days, no local; drug stopped, rib resected	Empyema cured 21 days after rib resection
Parent. 3,510,000 U. in 18 days, no local; rib resection 7th day of drug	No improvement until rib resection, then rapid
Parent. 7,500,000 U. in 6 days, local 290,000 U. 6 taps; rib resection	No improvement until rib resection, then rapid
Parent. 17,550,000 U. in 90 days, local 380,000 U. 12 taps; rib resection	No improvement until rib resection, then slow
Parent. 1,790,000 U. in 12 days, local 120,000 U. 10 taps; rib resection	No improvement until rib resection
Parent. 11,883,000 U. in 60 days, local 390,000 U. 11 taps; closed, then open drainage	Unimproved until rib resection
Parent. 17,405,000 U. in 84 days, local 75,000 U. 3 taps; rib resection	Unimproved until rib resection
Parent. 12,600,000 U. in 65 days, local 100,000 U. 2 taps; rib resection	Little improvement until rib resection
Parent. 1,775,000 U. in 16 days, local 160,000 U. 8 taps; rib resection	Little benefit until rib resection
Parent. 5,280,000 U. in 38 days; closed thoracotomy	After sulfonamides failed, healed on penicillin
Parent. 6,400,000 U. in 33 days; sulfonamide (blood level 13) without benefit	Prompt improvement, clinical cure within 1 mo.
Parent. 4,545,000 U. in 31 days; beginning to improve even before penicillin	Rapid regression to clinical cure
Parent. 4,915,000 U. in two courses, 19 and 7 days respectively	First abscess cured; 2nd abscess rapidly resolving
Parent. 4,800,000 U. in 39 days; had been considered malignancy	Dramatic and rapid clinical cure
Parent. 10,445,000 U. in 34 days; was being prepared for lobectomy	Rapid subsidence of fever and sputum to normal; arrested
Parent. 14,360,000 U. in 53 days (same patient as Case 2, Table VII)	Still asymptomatic after 6 mo.; small cavities still seen by x-ray
Parent. 4,402,000 U. in 28 days; pneumothorax from 1st stage drainage	No significant benefit; cured following pneumothorax
Parent. 9,165,000 U. in 38 days; 2 stage drainage, inadequate	No benefit; went to lobectomy (see below)
Parent. 10,020,000 U. in 51 days; 1st stage drainage of abscess	Some reduction in sputum, no change in x-ray picture
Parent. 5,885,000 U. in 30 days; rib resection 4 days before starting drug	Probably saved patient's life; returned to limited duty
Parent. 11,275,000 U. in 58 days; lobectomy and later rib resection for empyema	Developed putrid empyema, but recovered
Parent. 7,700,000 U. in 40 days; thoracotomy three times	Recovery with good re-expansion left upper lobe
Parent. 7,435,000 U. in 47 days, local 50,000 U.; lobectomy and later thoracotomy	Developed putrid empyema but recovered
Parent. 5,825,000 U. in 30 days; lobectomy after 20 days conservatism	Per primam healing of wound and uneventful recovery
Parent. 3,400,000 U. in 12 days, local 100,000; lobectomy, left lower lobe	Well into convalescence; had minimal empyema

little progress, other than a feeling of increased well-being, was made until rib resection. Of the larger series only three escaped surgery. At another hospital one of these patients was given penicillin at three-hour intervals for four months as the alternative to rib resection. The other two did not appear to have true empyemas in that only thin fluid containing streptococci was yielded. It will be observed that one patient (Case 1) developed empyema while receiving penicillin for Type I lobar pneumonia; yet rapid healing followed rib resection after stopping the drug. Although it is not shown in Table VIII, one patient (Case 6) failed to make satisfactory progress on penicillin plus a poorly draining closed thoracotomy. Prompt response followed rib resection. Likewise, patients (Cases 4 and 8) with rib resections done and receiving 200,000 units penicillin daily experienced temporary flare-ups when drainage became partly blocked and then returned to normal when this was corrected. In five cases, or 50 per cent, although the empyema was promptly sterilized on local and parenteral injections, pus continued to form and at rib resection 1,000 to 2,000 c.c. were evacuated. Our observations in this and in the larger series seem to show that penicillin is useful in empyema in controlling early systemic infection or accompanying pneumonia. However, if pus continues to form and is not satisfactorily decreasing within ten to fourteen days on parenteral and local penicillin and repeated aspirations, rib resection should be done without further delay, if mediastinal stabilization is adequate. Every effort should, of course, be made to diagnose empyema in its earliest phase when there will be reasonable likelihood of aborting the process by parenteral and local penicillin injections together with repeated aspirations.

A preliminary controlled study was also made of the effect of parenteral penicillin upon the final healing of empyema following rib resection. Four patients were placed upon parenteral penicillin (25,000 units intramuscularly every three hours) from the time of operation until their cavities had shrunk to less than 10 c.c. capacity and the tubes were removed. Five comparable and unselected patients, during the same season (February to June, 1944), receiving no penicillin, served as controls. The only other difference in the management of the two groups was that the test patients, kept on the penicillin ward, received an unusually high protein and vitamin diet and in addition averaged 2,000 c.c. of blood and 350 c.c. of plasma each during the study period, while only one blood transfusion was given to the entire control group. With exception of one penicillin-treated patient, however, whose red cells numbered 3,850,000 and hemoglobin 70 per cent, all patients of both groups had red counts over 4,100,000 and hemoglobin values of 80 to 85 per cent. Cultures of three test cases revealed beta hemolytic streptococcus and one pneumococcus; of the controls, one cultured pneumococcus, two beta hemolytic streptococcus, and one probable beta hemolytic streptococcus and one alpha hemolytic streptococcus. The comparable data are shown here:

	AVERAGE DURATION UNTIL THORACOTOMY (DAYS)	AVERAGE INITIAL SIZE OF CAVITY (C.C.)	AVERAGE DAYS UNTIL TUBE OUT
Penicillin cases	44	1625	119
Control cases	41	1300	156

Clinically the only noticeable difference between the experimental and control cases was a definite reduction in the growth of granulation tissue around the drainage tube in the penicillin cases. Trimming or cauterizing of these excess granulations was repeatedly necessary in the control patients but only once in a test patient. This inhibition of granuloplasia by the agent we have noticed elsewhere and Florey and Williams[21] have observed it in penicillin-treated infections of the hand. The lessening of morbidity shown in this small series is perhaps suggestive enough to warrant further study. However, until practical methods are worked out of maintaining effective penicillin levels by fewer injections, the lessened healing time will scarcely justify the prolonged needling of the patient.

Lung abscess without lobectomy (Cases 11 through 19, Table VIII): The deciding factor as to cure in cases of lung abscess without lobectomy seemed to be the degree of thickening and noncollapsibility of the cavity wall. Nor was this predictable entirely upon the duration of the lesion since two of the most responsive patients (Cases 14 and 15, Table VIII) had had symptoms for four and five and one-half months, respectively. It is our impression that penicillin is definitely superior to the sulfonamides in treating lung abscess and that relatively early and not too large abscesses will yield to the new drug in the great majority of cases without drainage. An interesting situation developed in several cases, notably 12, 14, 15, and 16, Table VIII, in which there was clinical cure but persistence of small nonactive cavities by x-ray. A soldier (Case 15) was being prepared for lobectomy but progressed so favorably on penicillin that he was, instead, sent out to limited duty for six months. It is too early to predict what the outcome will be in such lesions. The flora in nearly all the abscesses, for the most part obtained at bronchoscopy, was a mixture usually with alpha hemolytic streptococcus predominant. This culture usually persisted throughout regardless of the clinical course of the patient. Undoubtedly anaerobes were sometimes present in the abscesses and certainly in the putrid empyemas, although not detected by us.

Lung abscess with lobectomy: Of the 4 patients with lung abscess with lobectomy (Cases 18, 19, 20, and 21, Table VIII), two (Cases 18 and 19) had received thirty-seven and fifty-one days of intensive penicillin therapy before lobectomy with no significant improvement. One (Case 18) had had in addition, a two-stage drainage of the main abscess. Although the other (Case 19) proved to have an infected cyst, the surgical problem of its removal was similar to that presented by a chronic lung abscess. Penicillin was started in two instances (Cases 19 and 20) after lobectomy and as empyema was developing. In the other two (Cases 18 and 21) it was initiated nineteen and one days, respectively, before operation. Putrid empyema developed in all four cases but the patients survived. These four consecutive survivals, although of no statistical significance, are clinically important especially when it is realized that in the past lobectomy for chronic lung abscess carried a mortality in the neighborhood of 50 per cent.

Bronchiectasis with lobectomy: One patient (Case 10, Table IX) was saved by penicillin from a probable fatality following the development of pyopneumo-

thorax after sulfonamides had been unavailing. But the drug had no significant effect upon his underlying bronchiectasis. Nor did several weeks of treatment influence the bronchiectasis in Case 22. This is just as one might expect, considering the anatomic basis of the disease. Therefore, both patients were subjected to lobectomy under protection of heavy penicillin dosage. Both healed without developing empyema.

Penicillin in Intrathoracic "Medical" Disease.—

Pneumococcus lobar pneumonia: Six patients with pneumococcus pneumonia were treated with doses varying from 390,000 to 1,650,000 units. The duration of infection prior to penicillin ranged from one to six days with an average of three days. Three patients had shown no improvement despite adequate sulfadiazine therapy. Temperature returned to normal in from twelve to seventy-two hours (average thirty-six hours) following institution of penicillin therapy. In three cases sputum was sterile on culture as early as twenty-four hours after penicillin was begun. Blood cultures remained sterile in all cases. No complicating empyemas occurred. Larger doses than are ordinarily employed were considered necessary in the majority of these patients because of the duration of the infection prior to treatment or the absence of response to sulfadiazine. Tillet, Cambier, and McCormack[22] have worked out to a nicety the minimum dosage and treatment days required to cure lobar pneumonia.

Acute staphylococcal pulmonary infections: With the exception of one patient (Case 8, Table IX) all the members of the group with staphylococcal infections were exceedingly toxic and desperately ill (in fact one, Case 11, was moribund) when penicillin was started. In all cases sulfonamides had either failed or were producing no clinical improvement. Penicillin undoubtedly saved the lives of three patients (Cases 7, 9, and 10) and probably one other also (Case 8). In two (Cases 7 and 8) the temperature returned to normal within seventy-two hours and the clinical improvement was phenomenal.

When penicillin was started in one patient (Case 10, Table IX) he presented patchy consolidation of the entire right lung and a serosanguineous pleural effusion. Under therapy, temperature returned to normal on the twentieth day and all parenchymal lesions passed through the stage of multiple small cavities to complete disappearance to x-ray. The pleural effusion after temporarily loculating was reabsorbed, and did not become infected (fluid penicillin level 0.078 Oxford units). A patient (Case 11) treated at another hospital, under our direction, might possibly have been saved if penicillin had been started earlier.

Streptococcal pulmonary infections: The latter two of the three cases are presented in some detail.

CASE 13 (Table IX).—The patient was growing more critically ill in spite of adequate sulfadiazine therapy, and presented the picture of overwhelming generalized sepsis: bilateral bronchopneumonia, septicemia, widespread erythematous and hemorrhagic manifestations, left pleural effusion, and physical and electrocardoigraphic evidence of pericarditis with effusion. Forty-eight hours after the start of penicillin there was remarkable im-

provement and by the tenth day the temperature had dropped from 105.5 to 99.0° F. Within this time the right lung had completely cleared, though some pneumonitis may well have persisted within the left lung, obscured and compressed by the pleural effusion. Characteristically the left pleural effusion, although culturally sterile throughout, developed into empyema with high spiking fever, in spite of vigorous parenteral therapy and two 40,000 unit local injections. Final subsidence of fever and infection was much delayed even after rib resection and continued parenteral penicillin. The reason for this was never discovered.

CASE 14 (Table IX).—This patient was started on treatment twelve hours after the onset of illness. Dysphagia disappeared in twenty-four hours; tonsillar exudate cleared in forty-eight hours. On the fourth treatment day, the patient expectorated large quantities of purulent sputum containing fibrinous bronchial plugs culturing alpha hemolytic streptococci and rapid recovery followed.

Chronic pulmonary disease: In both of the patients (Cases 15 and 16, Table IX) with chronic bronchitides, anatomic changes in the bronchial tree had advanced so far that even had all bacteria been destroyed, reinfection would have been inevitable.

Penicillin in Subacute and Acute Septicemia.—

Subacute bacterial endocarditis: Our own nine-month remission (Case 2, Table X), the apparent success in fifteen out of twenty cases in Dawson and Hunter's series,[23] and the remissions in seven cases reported by Loewe and co-workers[24] bring new hope for cure of subacute bacterial endocarditis.

One patient (Case 1) died of cardiac failure although the blood stream remained sterile during penicillin treatment.

In contrast, another patient (Case 2, Table X) started on the drug the tenth day following the onset of subacute bacterial endocarditis responded very nicely. Blood cultures were sterile twenty-four hours after penicillin was begun, but five days after the completion of a thirty-day course they were again positive. Therapy was then given for an additional sixty-three days intramuscularly and also by the intravenous and subcutaneous drip method. Nine months after therapy there was no evidence of recurrence.

These two cases suggest, first, the importance of early diagnosis and commencement of penicillin treatment, and second, that a relapse after the completion of a month or more of treatment, granted the organism is reasonably penicillin susceptible, demands further trial and perhaps larger dosage of the drug.

Acute septicemia (Cases 3 to 13, Table X): Most of the cases of acute septicemia have been presented elsewhere in this paper. The proteus septicemia (Case 12) was treated before a positive blood culture was obtained and is no exception to the known resistance of this organism to penicillin. The only two fatalities among the remaining ten patients (Cases 5 and 11) were practically moribund when penicillin was started.

Penicillin in Intra-abdominal Suppuration.—This short and heterogenous series teaches us little about the effect of penicillin upon these infections. In the desperately ill patients (Cases 1 and 2, Table XI) the drug seemed definitely superior to sulfonamide therapy. This was also true in Cases 6 and 7,

TABLE IX. PENICILLIN IN INTRATHORACIC MEDICAL DISEASE

CASE NO.	AGE (YR.)	DIAGNOSIS	CULTURE	PENICILLIN TREATMENT	RESULTS
			Pneumococcal Lobar Pneumonia		
1	42	Pneumonia lobar, right upper lobe	Sputum, Pneumococcus type III	1,650,000 U. I.M.* in 8 days	Temperature normal in 72 hr.; recovered
2	21	Pneumonia lobar, right lower lobe	Sputum, Pneumococcus type XXVII	1,375,000 U. I.M. in 7 days	Temperature normal in 72 hr.; recovered
3	34	Pneumonia lobar, left upper lobe	Sputum, Pneumococcus type V	1,225,000 U. I.M. in 7 days	Sulfadiazine for 4 days without improvement, temperature normal in 19 hr.; sputum negative after 48 hr.
4	30	Pneumonia lobar, left lower lobe	Sputum, Pneumococcus type IV	470,000 U. I.M. in 5½ days	Temperature normal in 21 hr.; sputum negative in 24 hr.; recovered
5	35	Pneumonia lobar, right lower lobe	Sputum, Pneumococcus type I	1,150,000 U. I.M. in 6 days	Sulfadiazine ineffectual; temperature normal 12 hr. after penicillin started
6	22	Pneumonia lobar, right lower lobe	Sputum, Pneumococcus type VIII	390,000 U. I.M. in 4½ days	Sulfadiazine ineffectual; temperature normal in 24 hr.; sputum negative in 24 hr.
			Acute Staphylococcal Pulmonary Infections		
7	32	Infarcts both bases from severe ulcerative tonsillitis	Sputum, hem. Staph. aureus; alpha hem. Str.	3,130,000 U. I.M. in 25 days	Sulfadiazine ineffectual, patient toxic and stuporous; penicillin probably lifesaving
8	29	Infarct and pleuritis, left lower lobe and septicemia from otitis media	Blood, sputum and otitis media; hem. Staph. aureus	1,285,000 U. I.M. in 8 days	Sulfadiazine ineffectual; resolution of infarct and pleural effusion and blood stream sterile by 8th day
9	26	Multiple infarcts both lungs from severe orbital cellulitis	Furuncle, left nostril; hem. Staph. aureus	4,960,000 U. I.V.† and I.M. in 22 days	Sulfadiazine ineffectual, infarcts resolved; cavernous thrombosis averted
10	22	Pneumonia, entire right lung	Sputum, hem. Staph. aureus	8,460,000 U. I.V. and I.M. in 42 days	Sulfadiazine ineffectual; penicillin saved life and kept pleural effusion sterile
11	19	Bilateral pneumonia with abscess formation, septicemia	Blood and sputum; hem. Staph. aureus	925,000 U. I.V. and I.M. in 4 days	Sulfonamides for 10 days without improvement, patient then nearly moribund; died
			Streptococcal Infection of Lung and Pleura		
12	48	Pneumonia, left lower lobe	Sputum, alpha hem. Str.	580,000 U. I.M. in 5 days	Penicillin began 48th hour of disease and temperature became normal 72 hr. later
13	18	Bilateral pneumonia, empyema, pericarditis, bacteremia	Sputum, beta hem. Str.; blood alpha hem. Str.	2,830,000 U. I.M., 80,000 U. local	Saved life after sulfadiazine failed; later required more penicillin and thoracotomy to cure complicating empyema
14	36	Severe purulent bronchitis with ulcerative tonsillitis	Throat and sputum; alpha and beta hem. Str.	720,000 U. I.M. in 5 days	Within 48 hr. temperature normal, tonsillar exudate and dysphagia had disappeared
			Chronic Pulmonary Disease		
15	69	Chronic bronchial asthma due to bacterial sensitivity	Sputum, alpha hem. Str.; plus other bacteria	3,210,000 U. I.M. in 13 days	No significant alteration of symptoms or of the mixed flora in sputum
16	25	Chronic purulent bronchitis and mild bronchiectasis	Bronchial, nonhem. Str.; alpha Str. salivarius	4,890,000 U. I.M. in 26 days	No significant change in bronchial flora, sputum output, or cough

*I.M., intramuscular.
†I.V., intravenous.

*I.M., intramuscular.
†I.V., intravenous.

TABLE X. PENICILLIN IN SUBACUTE AND ACUTE SEPTICEMIA

CASE NO.	AGE	DIAGNOSIS	BLOOD CULTURE	PENICILLIN TREATMENT	RESULTS
			Subacute Bacterial Endocarditis		
1	5 yr.	S.B.E.* with patent interventricular septum and aortic insufficiency	Alpha hem. Str., microaerophilic, susceptible to .04 U.	2,460,000 U. I.M.† in 32 days	Blood culture sterile after 5 days but again positive when treatment stopped; died of cardiac failure
2	23 yr.	S.B.E. with rheumatic heart disease and aortic insufficiency	Alpha hem. Str. susceptible to .025 U.	18,000,000 U. in 96 days	One relapse after 30 days' therapy, drug restarted; 9 mo. cure, returned to duty
			Acute Septicemia		
3	27 yr.	Lobar pneumonia, left lower, empyema	Pneumococcus, type I	1,650,000 U. I.M. in 14 days	Recovery after drainage of empyema by rib resection
4	29 yr.	Septic pulmonary infarct from furunculosis of auditory canals	Hem. Staph. aureus	1,285,000 U. I.M. in 8 days	Recovered after he had developed osteomyelitis of ilium and sacroiliac joint
5	19 yr.	Bilateral staphylococcal pneumonia	Hem. Staph. aureus	925,000 U. I.M. and I.V.‡ in 4 days	Overwhelmed by the massive lung infection; died
6	18 yr.	Bilateral pneumonia, empyema, left, pericarditis	Alpha hem. Str.	2,830,000 U. parent.,§ 80,000 U. local	Recovery after drainage of empyema by rib resection
7	31 yr.	Primary source unknown	Hem. Staph. aureus	645,000 U. I.V. in 13 days	Blood stream sterilized in 24 hr.; afebrile 9 days after start of treatment
8	24 yr.	Pneumonia, empyema	Str. viridans	2,940,000 U. I.M., 490,000 U. local	Blood stream sterilized in 24 hr.; sulfonamide drugs had failed
9	38 yr.	Cholangeitis and liver abscess	Str. viridans	1,965,000 U. I.M. in 27 days	Saved patient's life when sulfonamides had failed
10	4 mo.	Acute ethmoiditis and osteomyelitis left humerus	Hem. Staph. aureus	443,000 U. I.M. in 30 days	Ethmoiditis cleared and osteomyelitis became inactive
11	22 yr.	Acute mastoiditis, and meningitis	Beta hem. Str.	625,000 U. I.M. in 3 days	Blood stream sterilized but developed pulmonary edema; died
12	25 yr.	Old osteomyelitis of left femur	Bacillus proteus	810,000 U. I.M. in 2½ days	Treated before the blood culture report returned; died
13	19 yr.	Osteomyelitis of left upper femur and septic arthritis of hip joint	Hem. Staph. aureus	Parent. 2,460,000 U. in 32 days	Systemic sepsis rapidly controlled but poor result locally

*S.B.E., subacute bacterial endocarditis.
†I.M., intramuscular.
‡I.V., intravenous.
§Parent., parenteral.

Table XI, two early and large appendiceal abscesses almost constituting localized peritonitis. Both patients had smooth postoperative courses in spite of surgical intervention during the most dangerous period of the disease. These results are encouraging and are in accord with the interesting animal experiments conducted by Fauley and associates,[25] in which they found that appendical peritonitis in dogs carrying a 50 per cent mortality when treated by sulfonamides showed 0 mortality when penicillin was started within one hour of the operation and 21 per cent mortality when penicillin was begun twelve hours after the appendix-ligating operation. Regardless of the numerous gram-negative organisms present in appendical peritonitis, the streptococci and anaerobes are undoubtedly of chief importance in pathogenesis. In controlling these, penicillin greatly increases the body's defenses. It is not surprising that where fecal leakage persisted, as in Case 4, Table XI, and in two other later cases observed by one of us (J. E. H.), even large doses of penicillin were of no avail.

Penicillin in Liver Abscess.—With the exception of the patient (Case 4, Table XII) who was not started on penicillin until exhausted by sixteen days of high fever and sepsis, our results in these few cases are highly encouraging. A patient (Case 2, an early one) receiving only 80,000 units a day would have responded, in our opinion, more promptly to 120,000 to 200,000 units. Case 3 (see penicillin chart, Fig. 6) is here presented in detail.

An 18-year-old soldier, a patient of Lieutenant Colonel J. R. Wells in consultation with us, was admitted to the Station Hospital, Fort McClellan, with a probable localizing appendiceal peritonitis. He grew rapidly worse despite vigorous sulfadiazine therapy and multiple transfusions. When penicillin was finally started, the patient was semistuporous, having five violent chills a day. He was jaundiced and the liver was four fingerbreadths below the costal margin and tender. The spleen was readily palpable. Striking improvement was noted within twelve hours and there was abrupt cessation of chills. Recovery was rapid. A single temperature spike to 103° F. on the tenth penicillin day was thought to be a reaction to a blood transfusion.

Penicillin in Nonveneral Genitourinary Infections.—Genitourinary infections suitable for penicillin therapy and study are uncommon both because the associated mechanical factor usually overshadows the infection, and also because the infecting organisms usually are nonamenable to the drug or are low-grade staphylococci hardly distinguishable from contaminants. The cases presented in Table XIII prove nothing. Even the two patients with sustained symptomatic improvement (Cases 1 and 2, Table XIII) showed no bacteriologic reason for this.

Penicillin in Dermatologic Infections.—

Sycosis vulgaris: Two patients (Cases 1 and 2, Table XIV) had previously received without benefit practically all known remedies including x-ray and sulfonamides. The first failed to respond to intensive combined local and parenteral penicillin, whereas the second finally responded to prolonged heavy parenteral treatment combined with local applications of penicillin in glycerin. No generalizations can be made here except that prolonged massive dosage may succeed when small or moderate ones fail.

Deep acne vulgaris: Cases 3 and 4, Table XIV, demonstrate to our satisfaction that large dosages (up to 45,000 units every three hours) are unavailing against infection superimposed upon a distorted, scarred and cystically-dilated sebaceous apparatus. In these two cases, however, multiple excision of infected cysts and nodules, and primary suture, during administration of parenteral penicillin, resulted in satisfactory per primam healing.

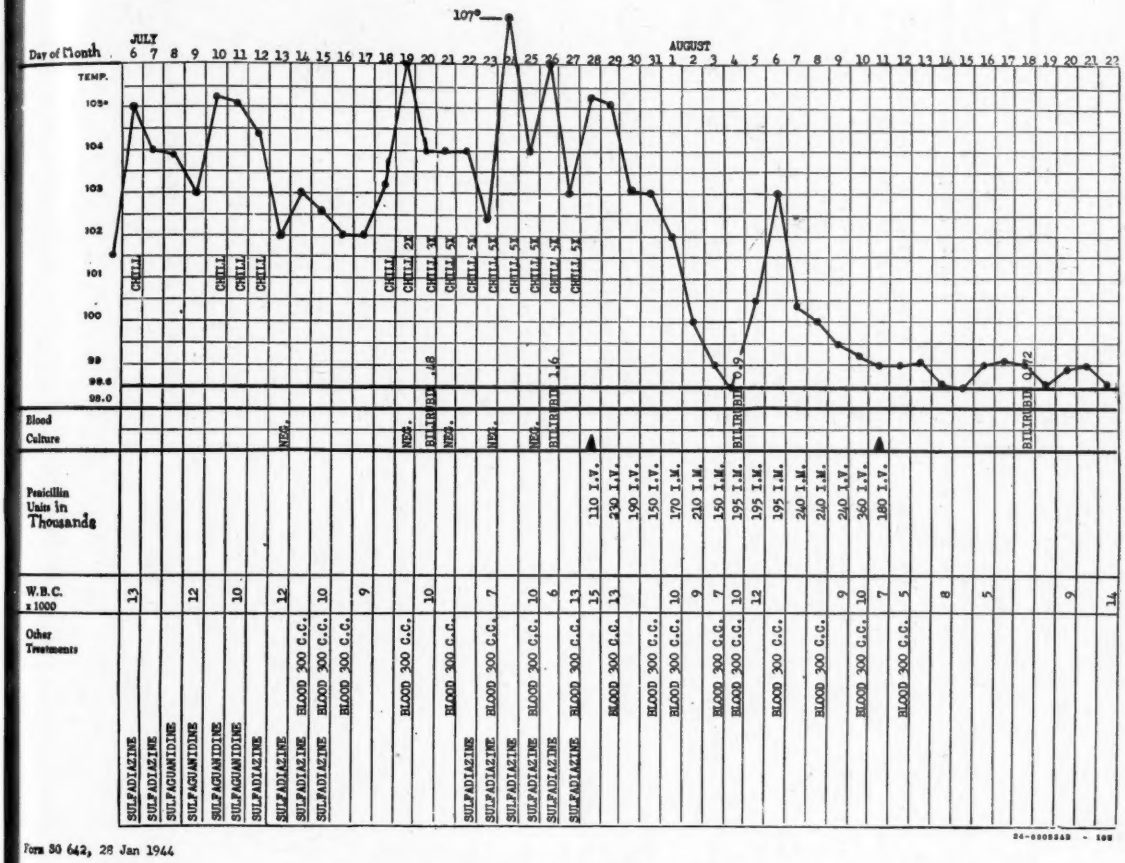


Fig. 6.—Graphic penicillin chart, Case 3, Table XII.

Pustular bacterid (Andrews): In Case 5 appreciable improvement was noted seventy-two hours after institution of penicillin therapy. Improvement obtained after eight days of treatment was equal to that obtained after three weeks of sulfathiazole. The sulfonamide had produced a severe toxic reaction and was therefore no longer available to this patient. Although a longer period of treatment was considered advisable, the patient refused to remain under observation any longer so that final appraisal was not permitted.

Penicillin in Miscellaneous Infections.—

Actinomycosis: We treated two patients with closely similar cases of actinomycosis of the tissues about the angle of the jaw of twenty-nine and twenty-

TABLE XI. PENICILLIN IN INTRAPERITONEAL SUPPURATION

CASE NO.	AGE (YR.)	DIAGNOSIS	BACTERIOLOGY	TREATMENT	RESULTS
1	27	Generalized peritonitis from infected abortion; bronchopneumonia	Str. faecalis; B. coli	Sulfonamide therapy unavailing, parent.* 7,400,000 U. in 36 days; pelvic abscess drained	Apparently lifesaving; afebrile 30th day
2	47	Generalized peritonitis from ruptured appendix; bronchopneumonia	Initial, alpha hem. Str.	Sulfonamide therapy unavailing, parent. 2,480,000 U. in 14 days; pelvic abscess drained	Rapid localization; afebrile 10th day
3	34	Generalized peritonitis from ruptured appendix	Gram-positive cocci and aerobacter. aerogenes	Parent. 10,240,000 U. in 43 days; no surgery	Slow recovery; afebrile 35th day
4	44	Generalized peritonitis from fecal leakage at biopsy site in colon	Lost	Parent. 720,000 U. in 3 days; leak in colon remained unrepaired	Fulminating exitus 5th day
5	36	Postoperative upper abdominal peritonitis and duodenal obstruction	Beta hem. Str.; hem. Staph. aureus pyogenes	Parent. 1,205,000 U. in 7 days	Died of obstruction but peritoneum sterilized
6	21	Large early appendical abscess; 5 mo. pregnancy	Esch. coli	Parent. 2,520,000 U. in 7 days, appendectomy on 4th day of disease; local sulfonamide therapy	Rapid recovery; afebrile on 10th day
7	45	Early appendical abscess; early delirium tremens	Nonhem. Str., Esch. coli, diphtheroids	Parent. 1,200,000 U. in 8 days, appendectomy on 3rd day of disease; local sulfonamide therapy	Rapid recovery; afebrile about 10th day
8	21	Right subphrenic abscess; right diaphragmatic pleuritis (Cause ?)	Nonhem. Str.; hem. Staph. aureus	Sulfonamide therapy unavailing, parent. 840,000 U. in 14 days; right subphrenic drainage	Apparently lifesaving; afebrile 12th day
9	31	Retroperitoneal abscess due to fistula from descending colon	B. Friedländers, Saccharomyces	Sulfonamide therapy unavailing, parent. 1,150,000 U. in 8 days; wide drainage	Died; chemotherapy no effect

*Parent., parenteral.

TABLE XII. PENICILLIN IN LIVER ABSCESS

CASE NO.	AGE (YR.)	DIAGNOSIS	BACTERIOLOGY	TREATMENT	RESULTS
1	20	Hyperactive amoebic abscess, right lobe of liver, surgically drained	Positive amoebic complement fixation test	11,695,000 U. parenteral, plus local	Rapid subsidence of high temperature; No secondary infection, recovered
2	38	Multiple liver abscesses possibly from cholecystitis	Blood culture once positive for Str. viridans	1,965,000 U. I.M.* in 27 days	No response to sulfadiazine (blood levels 19 mg. %) or emetine; penicillin doubtless saved life
3	18	Pylephlebitis secondary to appendiceal abscess	Blood cultures all negative (probably sulfonamide effect)	3,050,000 U. I.M. and I.V.† in 13 days	Penicillin lifesaving when sulfadiazine had failed
4	48	Multiple abscesses of liver and spleen from appendiceal (?) abscess	Blood cultures sterile; abscess: B. coli, Str., Staph.	1,500,000 U. I.M. in 6 days	Penicillin begun after patient desperately ill for 16 days; died

*I.M., intramuscularly.
†I.V., intravenously.

TABLE XIII. PENICILLIN IN GENITOURINARY INFECTION (NONVENEREAL)

CASE NO.	AGE (YR.)	DIAGNOSIS	CULTURE	PENICILLIN TREATMENT	RESULTS
1	50	Chronic prostatitis of 14 mo. duration	Hem. Staph. albus before and after treatment	250,000 U. in 48 hr.	After sulfadiazine and neoarsphenamine failed, still completely relieved 5 mo. after penicillin
2	52	Chronic prostatitis	Hem. Staph. albus before and after treatment	1,620,000 U. in 12 days	After sulfathiazole and neoarsphenamine failed, still completely relieved 7 mo. after penicillin
3	32	Chronic vesiculitis and prostatitis	B. coli; Str. faecalis; microaerophilic Staph.	4,375,000 U. in 23 days	Temporary relief of symptoms but later recurrence just as with sulfonamides
4	23	Chronic vesiculitis and prostatitis with acute cystourethritis	Earlier, hem. Staph. albus; at start of treatment, negative	1,935,000 U. in 16 days	Temporary symptomatic relief but pyuria persisted until vasotomy
5	34	Old rupture of posterior urethra, incontinence, urethritis	Mostly negative; occasional Staph. and diphtheroids	2,175,000 U. in 12 days	No clinical or bacteriologic change
6	?	Chronic anterior urethritis	Hem. Staph.; nonhem. Str.	2,160,000 U. in 9 days	No significant change

TABLE XIV. PENICILLIN IN DERMATOLOGIC INFECTIONS

CASE NO.	AGE (YR.)	DIAGNOSIS	CULTURE	PENICILLIN TREATMENT	RESULTS
1	28	Sycosis vulgaris	Beta hem. Str.; hem. Staph. aureus	15,285,000 U. in 52 days + local	Failure, in spite of daily dosage up to 480,000 U. and later addition of local therapy
2	36	Sycosis vulgaris	Beta hem. Str.; hem. Staph. albus	14,560,000 U. in 60 days + local	14 days of 120,000 U. daily + local failed but infection finally yielded to 320,000 U. daily + local
3	23	Deep acne, severe, with infected cyst formation	Hem. Staph. albus; proteus	12,925,000 U. in 52 days	First 200,000 U., then 360,000 U. daily failed; surgery and penicillin succeeded
4	21	Deep acne, severe with infected cyst formation	Proteus, pyocyaneus; hem. Staph. aureus and albus	16,720,000 U. in 52 days	First 200,000 U., then 360,000 U. daily failed; surgery and penicillin succeeded
5	50	Pustular dermatitis, bacterid type (Andrews)	Hem. Staph. aureus coagulose positive; diphtheroids	1,185,000 U. in 10 days	Cleared except for residual scaling; patient refused further treatment, superior to sulfonamide

eight months' duration, respectively. Both presented indurated lumpy lesions with active sinuses. One patient received a three-week course of 6,720,000 units intramuscularly, during which all traces of the disease other than the scars disappeared. Three months later there was no evidence of recurrence. The second patient received a six-week course of 14,945,000 units with apparent cure, only to develop a proved recurrence one month later. Thereupon a suprahyoid block dissection was performed while the patient was receiving 40,000 unit doses every three hours. The wound healed per primam and penicillin was continued for twenty-four days postoperatively.

The difference in response of these two patients to penicillin suggests wide variability in susceptibility among the actinomyces. The prompt recurrence in the second case after apparent cure suggests that the fungus, sealed within the dense scar tissue of the lesion, is not accessible to the drug. It suggests also that the involved tissue should be radically excised whenever possible.

Suppurative parotitis: One would expect that suppurative parotitis usually caused by one of the pyogenic cocci and characterized, at least in its early stage, by nonsuppurative cellulitis, would respond readily to penicillin. In our two patients, both of whom received 25,000 units intramuscularly every three hours, response was dramatic.

CASE 1.—An otherwise healthy young sergeant had early moderate left parotitis culturing hemolytic *Staph. aureus* susceptible to .01 units and alpha hemolytic *Str. salivarius* susceptible to .0012 units. Temperature and tenderness subsided in twenty-four hours and resolution was complete in ninety-six hours.

CASE 2.—A 59-year-old patient, hypertensive, with renal failure and severe azotemia (B.U.N. 97) developed over two days' time a large, very painful and exquisitely tender, hot swelling of the right gland. Complete relief of pain and definite reduction of swelling came within twelve hours and by the fifth day when therapy stopped, there remained only a small, nontender swelling. No drainage was noted, hence no culture was obtained.

Ulcerative colitis: Two patients with severe, chronic ulcerative colitis of 5 and 9 months' duration with typical roentgenologic findings and nonspecific stool cultures showed no improvement on penicillin therapy. One received 2,940,000 units over thirteen days, the other 6,806,000 units over twenty-eight days, as well as colonic irrigations of penicillin solution. The latter patient later showed improvement on sulfasuxidine.

Gonorrhea in women: Following the initial case, women with gonorrhea were turned over to Major Laman Gray, Chief of the Women's Surgery Section. An important observation was made by Gray in his twelve reported cases,[26] namely, that although the local and systemic infection was rapidly controlled, almost invariably the patient was left with bilateral tubo-ovarian masses and, therefore, with a prospect of probable sterility. In the case here presented the small tubo-ovarian abscesses might have been overlooked but for the gynecologist's specialized touch.

A 22-year-old woman with severe, early gonorrheal peritonitis, apparently the initial infection, was given 15,000 units penicillin intramuscularly every three hours for seven days. The vaginal smear and culture were negative within twelve hours. Within forty-

eight hours the initial temperature of 102.8° F. returned to normal and the patient felt greatly improved. On the seventh day of treatment the patient was practically well, clinically, and vaginal cultures remained negative, but bilateral tubo-ovarian masses were made out by the gynecologist. The sedimentation rate was 19. At final discharge sixteen days later the tubo-ovarian masses were little changed but the sedimentation rate had dropped to 6.

Early syphilis: Our single case is presented briefly.

A 16-year-old white married woman was admitted to Walter Reed General Hospital with severe hemorrhagic encephalitis complicating neoarsphenamine therapy for early secondary syphilis. Kahn and Wassermann tests were both 4 plus. On Nov. 24, 1943, 30,000 units of penicillin intramuscularly at three-hour intervals were started and a total of 4,645,000 units were injected over a twenty-nine-day period. The serologic titers progressively weakened until by Feb. 9, 1944, both Kahn and Wassermann were negative. From recent careful work by Moore and associates[27] a much smaller dosage has been found effective in these cases.

Nephritis: Three patients with acute exacerbations of chronic glomerulonephritis received 25,000 units of penicillin every three hours for fourteen days, or a total dose per patient of 2,800,000 units. No significant alteration of the sedimentation rate, Addis count, urine albumin content, or renal function studies was noted during therapy or for the three months thereafter that the patients were under observation.

Rheumatic fever: Three patients with acute rheumatic fever were treated with intramuscular injections of penicillin for fourteen days, two patients receiving 25,000 units every three hours, the third receiving 45,000 units at similar intervals. There was no appreciable clinical improvement or change in the sedimentation rate. Others[28, 29] in more extensive studies have reached similar conclusions.

Tuberculosis: Although it is established[30, 31] that penicillin exerts no in vitro or in vivo effect upon the tubercle bacillus, it was thought advisable by some to make a clinical trial in two cases. Needless to say, neither patient showed any response to the drug. The first, with tuberculous meningitis, received 10,000 to 20,000 units intrathecally and 480,000 units intramuscularly each day for five days. The second patient with tuberculous pneumonia and pleural effusion, first suspected of coccidioidomycosis, received 3,220,000 units over a ten-day period.

Chronic brucellosis: Penicillin was administered over an eight- to ten-day period to two patients with chronic brucellosis. Blood cultures were sterile in both patients. Agglutination tests for *B. abortus* and *B. melitensis,* brucellergin skin tests, and opsonocytophagic indices were not significantly altered during or after treatment nor was there any clinical improvement in either case. One patient, an 11-year-old boy with periodic bouts of fever, received a total of 760,000 units in eight days. The second patient, who had secondary uveitis, was given 3,600,000 units over a ten-day period. Longer periods of therapy and larger doses are indicated before a final appraisal of the efficacy of penicillin can be made. Both *B. melitensis* and *B. abortus* have been found to be susceptible to penicillin in vitro.[30, 32]

Iridocyclitis: Our experience is limited to two cases.

(1) Uveitis secondary to focalized chronic brucellosis (noted previously) failed to improve after ten days of 45,000 units intramuscularly at three-hour intervals.

(2) Iridocyclitis, bilateral, slowly progressive, cause unknown, made no improvement after twenty-one days of intensive treatment totalling 4,955,000 units.

SUMMARY

1. A review is presented of the laboratory and clinical experience of the Walter Reed General Hospital penicillin committee from July, 1943, through September, 1944.

2. The analysis includes 255 conditions in 220 patients for which penicillin treatment was administered.

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A SAFETY FACTOR IN GASTRIC RESECTION

Preliminary Report

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A LIMITED but encouraging experience warrants this brief preliminary report upon a new device designed to reduce materially, if not to eliminate entirely, one of the most dangerous hazards of gastric resection—disruption of the duodenal stump.

Disruption of the duodenal stump following gastric resection and anastomosis by any one of the Billroth II modifications occurs often enough to make it a prominent feature in the surgical literature dealing with the treatment of gastric ulceration or malignancy. It is not our purpose to present a résumé of the literature in this initial report but rather to emphasize the danger of this complication, the very high mortality associated with it, and to stress a means for its prevention.

In my opinion, by far the most common cause of stump leakage is increased pressure within the duodenal lumen consequent upon obstruction, partial or complete, at the anastomotic site. In the best of hands, angulations and kinks at the stoma do occur. Individual variations and conditions found at operation require variations in technique. Hypoproteinemia with its consequent edema may play a part in closing a lumen otherwise competent. But from whatever cause arising, an obstruction of the proximal duodenum leaves no egress for the bile, pancreatic secretions, and the secretions of the duodenum itself, amounting to approximately 1,500 c.c. in twenty-four hours. This increased intraluminal pressure then seeks an alternative outlet which results in bringing too much stress to bear upon a stump however carefully it may have been sutured.

The T tube here reported and illustrated was designed primarily for usage in the Hofmeister-Polya type of anastomosis as elaborated and popularized by the Lahey Clinic. However, other models are available adapted for use in the Polya anastomosis where the entire cut end of the stomach is employed for union with the jejunum.

The tube is more easily illustrated than described, and a reference to Figs. 1 to 3 is all that is required. It is smooth of surface, presenting one vertical portion of the inverted T, which fits loosely into the gastric part of the stoma, and the other, the long curved horizontal portion, resting in the jejunum, one end of which extends well proximal and the other end of which extends well distal to the anastomotic site. At no point does the tube exert any pressure upon the bowel wall. It is inserted into the anastomosis after all but the suturing of the anterior wall of the stomach and jejunum has been completed. The tube is fastened into the stoma by a figure-of-eight suture passing through the posterior wall of the anastomosis and tied around the tube. This suture may be

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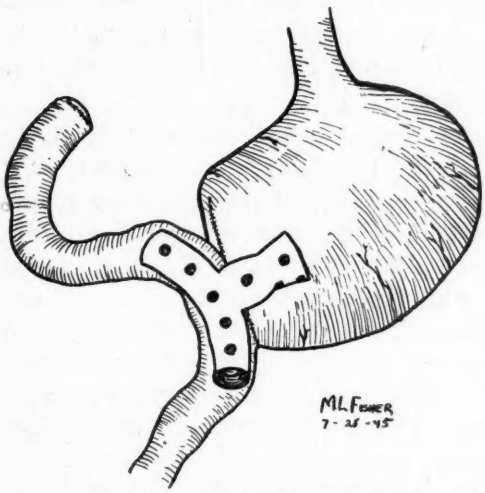
of silk or gastrointestinal chromic as desired. The anastomosis is then completed in the usual fashion.

Reference to the illustrations will show at once the obvious merits of this device. The multiple fenestrations encourage free flow of duodenal and gastric secretions into the distal jejunum and make it impossible for blocking to occur. The presence of the tube during the final stages of the anastomosis serves as a mold over which more accurate suturing can be performed and as a safeguard against kinks and angulations. Should postoperative edema occur, the tube prevents obstruction from this cause.



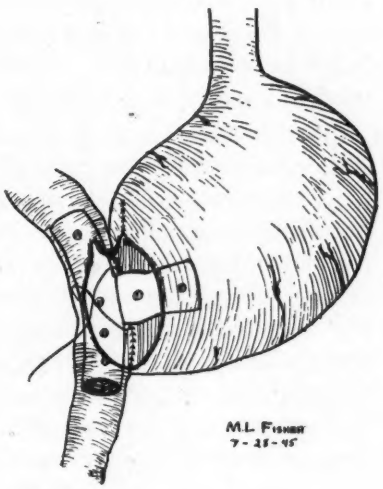


Fig. 1.—Diagrammatic representation of the T tube in position.
Fig. 2.—Diagrammatic representation of the T tube being placed loosely in the gastrojejunal stoma.

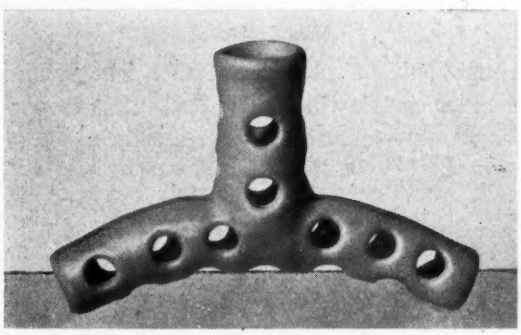


Fig. 3.—Photograph of the T tube.

As noted by Mr. Miller in a later portion of this article, the tube disintegrates within a period of about ninety-six hours, thus furnishing a dependable framework for the anastomotic stoma during that period when obstruction may occur, but dissolving and removing that framework when it is no longer required. Mr. Miller's extensive experience with this product enables him to time this disintegration quite accurately.

The use of this tube would in no manner preclude the use of the Abbott-Rawson tube at the same time. It is, however, my opinion that the T tube will obviate this necessity and will permit the discharge of liquids from the stomach into the distal jejunum very early postoperatively. Further experience is necessary to determine that point.

The following description of the chemistry and mechanics involved is furnished by Mr. Grover C. Miller, chemist of the Seal-Ins Laboratories, whose pioneer work on enteric coatings for tablets and capsules is well known.

"The Alesen T tube is a further development of the principle used in the timed enteric coating for tablets and capsules discovered by Grover C. Miller several years ago. The dependability of this coating has been proved by the following investigators: Worton, Kempf, Burrin, and Bibbins,[1] Wright and Brady,[2] Faust,[3, 5] and Miller and Choquette.[4]

"The material used in making these tubes* varies somewhat from the enteric coating, but the principle is the same. Percentages are changed to meet the timing requirements. These tubes are composed of the following: stearic acid, U.S.P., carnauba wax No. 1, white purified beeswax, petroleum jelly, powdered elm bark, and an antiseptic, merthiolate 1 to 7000. Also barium sulfate is combined in the mixture so it is possible to x-ray the patient at any time during the disintegration of the tube. This material has a melting point of approximately 85° C. The purpose of the powdered elm bark is to absorb water and expand; the expanding gradually splits away the waxes and permits a further penetration of the moisture into the wall. The timing is controlled by the percentage of elm bark used.

"The Alesen T tube is timed to disintegrate in approximately ninety-six hours. The tube may be sterilized by placing it in a zephiran chloride solution, 1 to 1000, for fifteen minutes at room temperature.

HOW MADE

"The tubes are molded in 55, 60, and 65 mm. lengths on a 6 mm. rod curved to 115 mm. circle. The gastric tip of the T is molded on a 11 mm. rod. The gauge of the wall is of approximately 2 mm. thickness."

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*The T tubes may be obtained from the Seal-Ins Laboratories, Los Angeles, Calif.

HYPERURICEMIA IN GASTRIC CANCER

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THE value and significance of an adequate protein balance to the surgical patient have been studied by many authors on innumerable occasions. In previous studies that I did with Adams[1, 2] we were able to differentiate hypoproteinemia secondary to insufficient dietary protein from hypoproteinemia secondary to accelerated endogenous protein depletion. This differentiation was made possible by an evaluation of blood uric acid.

Blood uric acid will rise in the presence of endogenous hypoproteinemia. This results from the patient's attempts to replenish his protein deficiency through endogenous protein secured from his own body. Clinically this state is revealed in the loss of strength and weight. Chemically it can be demonstrated in an elevation of uric acid. The greater the hyperuricemia the more accelerated is the rate of endogenous protein metabolism. The reason for the hyperuricemia is the fact that uric acid is one of the end products of endogenous protein metabolism.[2]

When uric acid is the end product of body purine metabolism it is called endogenous uric acid. The term endogenous is used to distinguish the uric acid formed from the purines produced in the course of the digestion of food proteins. Endogenous uric acid is derived from the breakdown of nuclear material found in muscle tissue and glandular structures. An increase in endogenous uric acid results in an elevation of blood uric acid (normal value taken is 3 mg. per 100 c.c. of serum). A uric acid value above this level is termed hyperuricemia.

In considering hyperuricemia, other causes for an elevated blood uric acid must be remembered. Primary liver disease may produce hyperuricemia if the disease process is sufficiently advanced to result in impaired hepatic physiology. Since uric acid destruction occurs in the liver a resulting hyperuricemia is easily understood. Renal failure also causes an early rise in blood uric acid. The status of the liver and kidneys can be determined by specific chemical tests directed at evaluating these organs. When the liver and kidneys are not primarily impaired, a pre-existing hypoproteinemia accelerates endogenous purine metabolism. This accelerated endogenous metabolism results in hyperuricemia. The significance of hyperuricemia is that it is an indicator of the degree of endogenous protein metabolic activity. Thus a graphic picture of the patient's nutritional state can be evaluated by a physiochemical analysis of the blood.[2]

In order to interpret adequately the relationship between serum protein and serum uric acid, both determinations must be performed simultaneously. It has been found that patients with gastric cancer usually have a lowered serum protein. This hypoproteinemia results because of a loss of appetite, especially for meat, and the fear of eating because of nausea and vomiting.

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TABLE I. PROTEIN AND URIC ACID VALUES IN GASTRIC CANCER PATIENTS WITH SLIGHT HYPERURICEMIA

CASE	AGE (YR.) SEX	SERUM PROTEIN	SERUM URIC ACID	WEIGHT LOSS (LB.)	PERIOD OF WEIGHT LOSS (MO.)
1	42 M	6.2	3.9	12	6
2	49 M	6.5	3.7	10	8
3	57 M	6.1	3.9	12	7
4	60 F	6.0	4.0	15	6
5	50 M	6.5	3.7	10	8
6	49 M	6.0	4.0	14	7
7	63 F	6.0	3.9	13	6
8	57 M	6.1	3.9	14	6

TABLE II. PROTEIN AND URIC ACID VALUES IN GASTRIC CANCER PATIENTS WITH MODERATE HYPERURICEMIA

CASE	AGE (YR.) SEX	SERUM PROTEIN	SERUM URIC ACID	WEIGHT LOSS (LB.)	PERIOD OF WEIGHT LOSS (MO.)
1	52 M	5.5	4.2	15	6
2	63 F	5.5	5.0	23	4
3	55 M	5.9	5.0	25	4
4	57 M	6.0	4.5	16	6
5	55 M	5.5	4.9	20	5
6	58 F	6.0	4.5	15	6

TABLE III. PROTEIN AND URIC ACID VALUES IN GASTRIC CANCER PATIENTS WITH MARKED HYPERURICEMIA INCLUDING POSTOPERATIVE COMPLICATIONS

CASE	AGE (YR.) SEX	SERUM PROTEIN	SERUM URIC ACID	WEIGHT LOSS (LB.)	PERIOD OF WEIGHT LOSS (MO.)	POSTOPERATIVE COMPLICATION
1*	56 M	5.0	5.0	25	4	Gouty arthritis
2	62 M	4.5	5.2	30	3	Bronchopneumonia and wound infection
3*	57 M	4.5	5.5	30	2	Gouty arthritis
4	62 M	4.5	5.4	25	4	Bronchopneumonia
5	67 M	5.0	5.0	25	4	Wound dehiscence
6	65 F	4.5	5.2	25	3	Bronchopneumonia and wound infection

*Cases previously reported elsewhere.[1]

The diet usually consists of simple fluids without adequate protein. The result is an inevitable progressive hypoproteinemia. Hypoproteinemia of this type usually is associated with a hyperuricemia. The lower the protein level, the higher will be the uric acid level.

A normal uric acid in the presence of a hypoproteinemia signifies that a sufficient amount of exogenous protein is available to prevent the utilization of endogenous protein. This indicates that sufficient protein is available to satisfy the basic protein requirements of the surgical patient with gastric cancer. An intelligent interpretation of blood uric acid in association with serum protein values will indicate the ratio between exogenous and endogenous protein metabolism. These studies have been employed in twenty patients with gastric cancer. From these studies a physiochemical prognostic guide to the nutritional state of the patient with gastric cancer was available. Current observations, discussion, and conclusions on hyperuricemia in gastric cancer follow. (See Tables I, II, and III.)

DISCUSSION

The majority of patients with gastric cancer have an alteration in their normal dietary regime. As the disease progresses complete loss of appetite may occur followed by an almost total abstinence of food because of nausea and vomiting. This results in an inadequate protein intake and a subsequent hypoproteinemia. The daily protein requirement can be determined from the amount of nitrogen eliminated in the feces and urine in twenty-four hours. This total nitrogen excretion per day multiplied by 6.25 will give the approximate amount of protein destroyed over twenty-four hours in the gastric cancer patient. An intake of protein equivalent to the protein destroyed in the body will usually suffice to keep the human body in positive nitrogen balance. This basic protein requirement for an average man (70 kg.) is 70 Gm. The present studies concern the gastric cancer patient who does not obtain this basic requirement of 70 Gm. of protein.

As has been previously stated, the lack of protein intake quickly results in a hypoproteinemia. The human body attempts to correct this disturbed physiologic state by calling upon the body protein. This stimulus accelerates endogenous protein metabolism with a subsequent increase in blood uric acid.

Current observations on this topic have led to the belief that a causal relationship exists between hyperuricemia and hypoproteinemia. This belief is founded upon many more studies of uric acid and protein than are presented here. An indication of the relationship between the two may be gleaned from Fig. 1.

Specific study of twenty patients with gastric cancer has corroborated the interrelationship between hyperuricemia and hypoproteinemia. We have divided these cases into three groups according to the degree of hyperuricemia. The terms mild, moderate, and marked are employed to identify each group.

The first group of eight patients had slight alteration in serum uric acid and the patients categorized as having mild hyperuricemia. The uric acid values ranged from 3.7 to 4 mg. per 100 c.c. of serum. Serum protein determinations were 6 to 6.3 Gm. per cent. This uric acid value is taken as the uppermost limit of normal, and the protein as the lowest normal level. Patients in this group appeared to have secured a harmonious balance between exogenous and endogenous protein metabolism. These patients had a diminished protein intake but no complete lack of exogenous protein. In this group weight loss was the least (ten to fifteen pounds) and extended over a period of from six to eight months. These patients had the best prognosis, the least postoperative complications, and were restored to positive nitrogen balance rapidly.

In the intermediate group, the six patients were categorized as having moderate hyperuricemia. The uric acid values in this group ranged from 4 to 5 mg. per cent with protein values of 5 to 6 Gm. Patients falling into this category gave a history of fifteen to twenty-five pounds loss of weight over a period of four to six months. In general these patients tolerated operation well after an adequate preoperative regime which included a correction

of the hypoproteinemia. Postoperative complications were infrequent and when present were of minor consideration.

Particular interest here concerns the last group of six patients who had pronounced hyperuricemia. These patients had insufficient protein intake which produced a hypoproteinemia. In order to compensate for this lowered protein level, protein was mobilized from the body tissues to rectify the hypoproteinemia. The serum uric acid level became elevated since it is an end product of endogenous protein metabolism. This accelerated endogenous

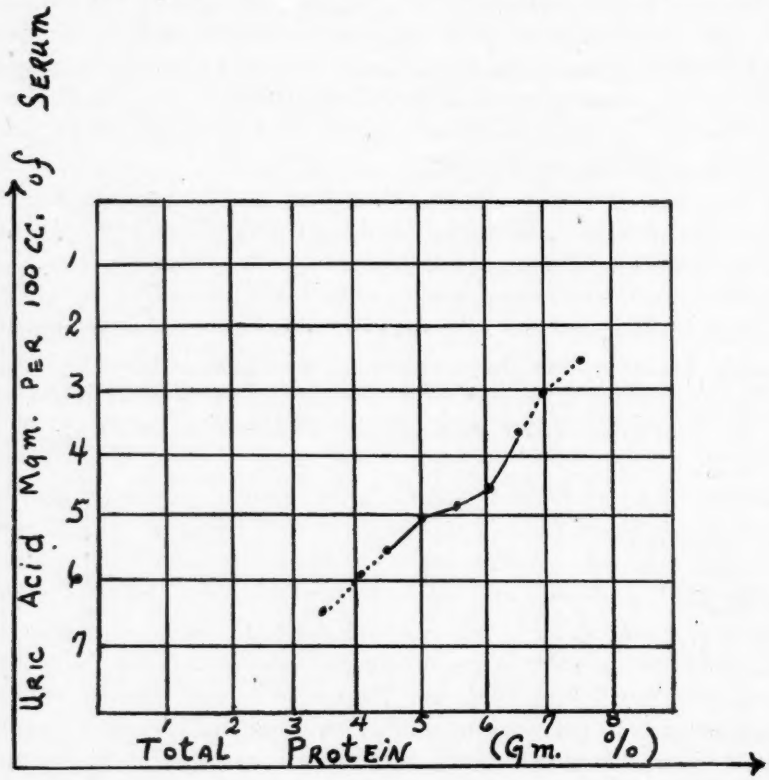

Fig. 1.—Graphic relationship between hyperuricemia and hypoproteinemia. Completed line indicates the relationship between total protein and uric acid values based upon cases presented. Incompleted lines suggest further ratio as revealed in other case studies.

protein metabolism was displayed clinically by a loss of twenty-five to thirty pounds over a period of two to four months. Accelerated endogenous protein metabolism of this type is characterized by a rapid loss of weight over a short period of time. Physiochemically it is demonstrated by a low protein and a high uric acid. In the six patients studied the serum protein fell to a level of 4 to 5 Gm.; the serum uric acid value rose to 5 and 5.5 mg. per cent.

Hyperuricemia as displayed by this group is significantly valuable as a prognostic guide to postoperative complications. Studies of many cases falling into this category, in addition to those discussed here, have indicated that most complications occur in patients with marked hyperuricemia. These

complications may be slight or severe. The most frequently encountered complications are:

1. Muscle weakness and fatigability
2. Nutritional edema
   (a) Edema of sacrum and ankles
   (b) Edema of anastomosis, stoma, and gastrointestinal mucosa
   (c) Delayed wound healing and/or wound dehiscence
   (d) Circulatory insufficiency
      (1) Diminished urinary output
3. Lowered resistance to infection
   (a) Wound infection
   (b) Postoperative pneumonitis
   (c) Urinary infections
4. Postoperative gouty arthritis

Of all the postoperative complications mentioned the most interesting is postoperative gouty arthritis. A definite pattern in the production of postoperative gouty arthritis cannot be stated without dispute. However, in a previous publication a pathway in the production of this complication was postulated.[1] The mechanism advanced was that in the presence of a hypoproteinemia, endogenous purine metabolism is accelerated. This accelerated metabolism results in a hyperuricemia which is the precipitating agent for the deposition of urate crystals on a previously damaged cartilaginous joint surface. In my report with Adams[1] of five instances of postoperative gouty arthritis, all patients had a varying degree of osteoarthritis. From this it can be appreciated that hyperuricemia may have a more far-reaching significance than is apparent at the present time.

Apropos of this statement, recent experimental publications on the effects of a low lysine diet on the growth of spontaneous mammary cancer may find some association with uric acid metabolism.[3] Briefly, this research has shown that the rate of tumor growth in mice can be inhibited for short periods of time when a diet is administered in which lysine is deficient. (Lysine, an essential amino acid, has been established as essentially a growth factor.) This is further substantiated by the rapid rate of tumor growth when lysine is added to the diet. On the basis of these observations it seems that neoplastic tissue, like normal somatic tissue, requires protein for growth.[3] It seems logical that this needed protein is taken from the protein reserves of the body. This was proved by the fact that the experimental animals had a marked weight loss.[3] Apparently this situation paralleled the loss of weight observed in the patients previously presented.

In view of this experimental observation on mice, another factor in the acceleration of endogenous protein metabolism appears to be at work producing a hypoproteinemia. This hypoproteinemia may be increased because a growing cancer will utilize the most readily available body protein. This new source of increased endogenous protein metabolism, in addition to other factors previously mentioned, will further increase the hyperuricemic state. Perhaps

additional future studies on hyperuricemia may bring to light some method of calculating the rate and extent of cancer growth.

SUMMARY

1. Attention is called to the significance of hyperuricemia in the exact evaluation of the nutritional state of patients with gastric cancer.

2. The importance of serum uric acid study in conjunction with serum protein determinations is stressed.

3. Twenty gastric cancer patients with alterations in serum uric acid and protein were studied and the results presented.

4. According to the degree of uric acid elevation, these patients have been categorized as having mild, moderate, or marked hyperuricemia.

5. Each group is discussed in terms of weight loss and the length of time over which the loss occurred. Emphasis is placed on those patients with marked hyperuricemia.

6. Many of the complications associated with hypoproteinemia and hyperuricemia, including postoperative gouty arthritis, were found in the group with marked hyperuricemia.

7. Mention is made of recent cancer research on the growth of cancer and the possible association of the rate of cancer growth with the facts presented here.

CONCLUSIONS

The present physiochemical analysis of twenty patients with gastric cancer coincides with the current study on the relationship between hypoproteinemia and hyperuricemia. This interrelationship indicates that a more complete evaluation of the nutritional state of the surgical patient can be obtained by studying the blood serum uric acid in conjunction with a serum protein determination. Heretofore it was believed that protein study alone was sufficient in evaluating the nutritional state of the body. It is hoped that the significance of hyperuricemia in patients with gastric cancer has been emphasized. The importance of hyperuricemia is stressed, first, because it differentiates hypoproteinemia subsequent to insufficient exogenous protein from hypoproteinemia resulting from accelerated endogenous protein metabolism. Thus, the exact source of protein depletion can be identified and corrected. Second, it will assist in foretelling postoperative complications usually associated with a debilitated nutritional state in patients with gastrointestinal cancer.

Many of the cases reported in this study were investigated by the author during his Fellowship in Surgery at the Lahey Clinic, Boston, Mass.

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MULTIPLE CARCINOMAS OF THE STOMACH

Case Presentation With Five Primary Separate Malignant Lesions Treated by Total Transthoracic Gastrectomy

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THERE has been a great deal of progress made in the technique and end results in transthoracic resections of the stomach since the first successful ones were done by Ochsner and DeBakey in 1938.[1-3] Although the abdominal route to total gastrectomy in most hands still offers less risk to the patient,[4-6] there are many lesions involving the lower end of the esophagus which cannot be attacked by this approach. The first successful total gastrectomy by the transthoracic route was done by Willy Meyer in 1942.[7] Since that time Sweet has reported eighteen cases with seven deaths, a mortality rate of 38.8 per cent, which results compare favorably to those resections done by the abdominal route.[8-11] The success of surgery of this magnitude in these debilitated patients depends on adequate preoperative preparation; rapid, careful surgical technique with expertly administered anesthesia; and careful postoperative care.

The occurrence of multiple benign lesions of the stomach has been reported several times, and, although multiple malignancies of the gastrointestinal tract are second most frequent to skin lesions,[12] multiple malignancies of the stomach are comparatively rare lesions. Walters, Gray, and Priestly[13] stated that malignant growths of the stomach are invariably single, but pointed out that frequently there is little to distinguish a malignant from a benign growth microscopically. Brindley, Dockerty, and Gray[14] reported twenty-three multiple malignancies of the stomach out of 1,184 carcinomas of the stomach seen at the Mayo Clinic between 1932 and 1941, an incidence of 1.94 per cent; and they reported an additional patient with four adenocarcinomas of the stomach. Owen[15] in 1921 reported a patient with four primary malignancies of the stomach. Of all patients with multiple primary malignancies at autopsy, multiple malignant lesions of the stomach occupy about 2.8 per cent.[12]

The case to be presented is doubly interesting in that the patient had five primary cancerous lesions of the stomach and he was treated by transthoracic gastrectomy.

CASE REPORT

H. G. (I 44 152199).—A 54-year-old Negro man entered Charity Hospital Sept. 19, 1944, complaining of pain in the epigastrium of four months' duration. The pain started while the patient was receiving anti-syphilitic therapy from his local physician. Once the pain started it remained as a constant burning pain which was not relieved by soda or food.

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He vomited at least once daily but not at any particular time of the day. During the four-month period his weight decreased from 125 to 103 pounds, a loss of twenty-two pounds. The past history was essentially negative. No primary syphilitic history was obtained.

Physical Examination on Admission.—The patient, of above average intellect, had no acute distress. Blood pressure was 84/?; temperature, 100.4° F.; pulse, 74; respirations, 20. The skin showed evidence of chronic dehydration. Head and neck were found essentially negative. In the chest, the lungs and heart were essentially normal. The abdomen was soft, with no masses, and slight guarding in the epigastrium. There were no scars.

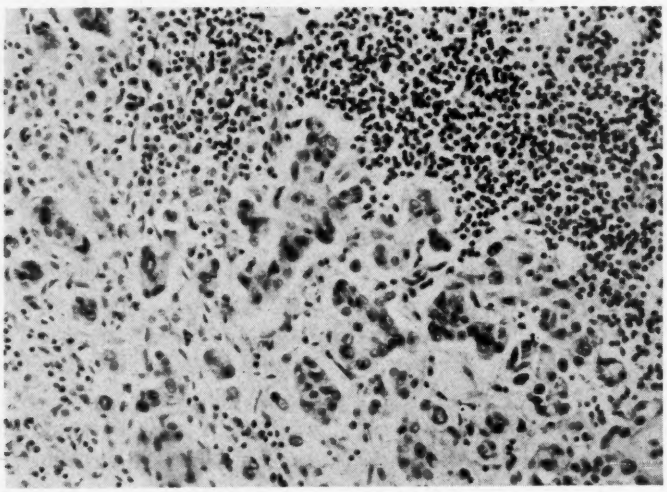

Fig. 1.—Lymph node from lesser curvature showing infiltration by adenocarcinoma (×200).

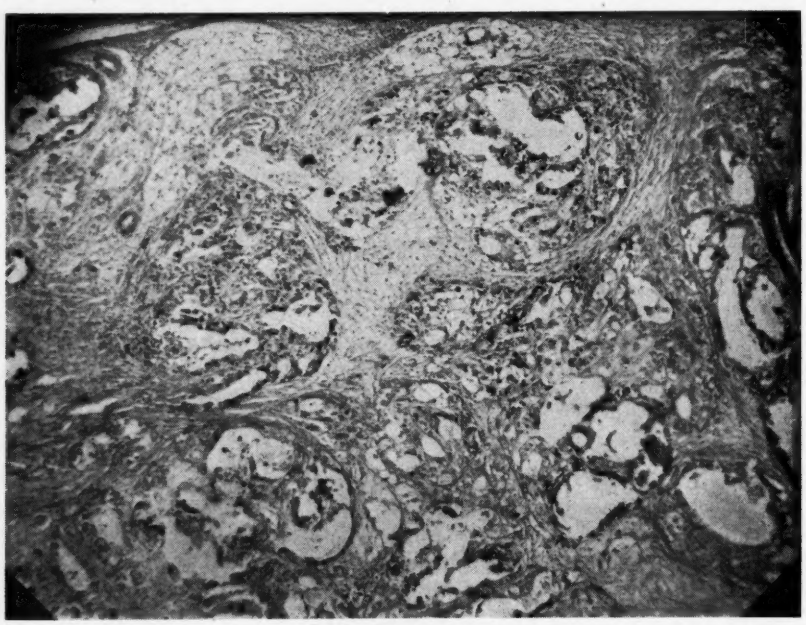

Fig. 2.—The first tumor, at the cardia, showing diffuse infiltration of the wall of the stomach by the neoplastic tissue (×61).

Genitals were normal. Rectal examination revealed no masses and no rectal shelf. Extremities and reflexes were normal.

The admitting diagnosis was carcinoma of the stomach.

Laboratory.—September 20, hemoglobin was 12 Gm.; white blood cells, 5,200; normal differential. Urine was essentially negative.

September 22, gastrointestinal series showed no abnormalities of the esophagus or duodenum. A small ulcer was found on the prepyloric portion of the stomach.

October 2, blood urea nitrogen was 8.7. Hippuric acid liver function test was normal.

The diagnosis remained carcinoma of the stomach despite the x-ray report.

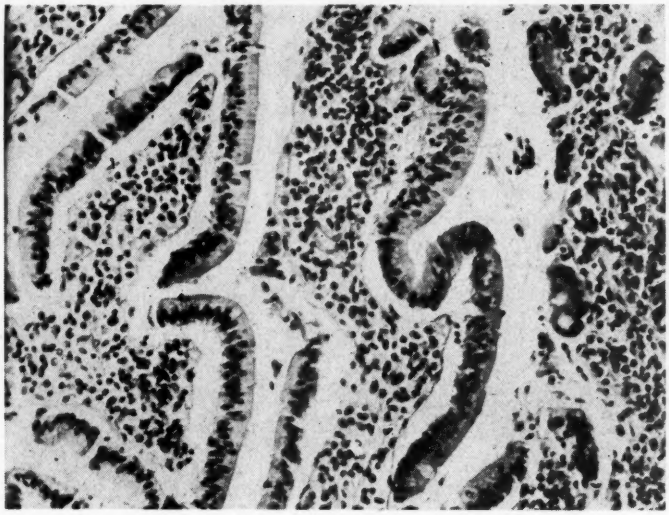

Fig. 3.—The second tumor in the body, showing junction of normal and malignant tissue; note tortuous malignant glands (×200).

Oct. 5, 1944, exploration was done through an upper midline incision. A large carcinoma of the cardia was found which had extended into the thoracic esophagus. A smaller very soft lesion was palpable at the pylorus which did not seem to involve the muscularis or the serosa over it. There were several small lymph nodes in the lesser omentum, but there were no palpable nodules in the liver. The greater omentum contained several small nodes at the pylorus but these were soft. The rest of the abdomen was thoroughly explored and was essentially normal. The stomach was then opened; the small soft lesion at the pylorus was biopsied and the stomach was then closed. The lymph nodes at the pylorus were removed and together with the biopsy of the lesion at the pylorus were sent for frozen section. The gastric lesion was reported as malignant and nodes showed no evidence of malignancy. It was obvious that any curative procedure would have to be done by the transthoracic route because of the extent of the lesion at the cardia. The stomach was then thoroughly mobilized by removing the greater omentum from the transverse colon and the lesser omentum from the liver. The left gastric, left gastroepiploic, and right gastroepiploic vessels were then ligated and divided near their origins, and the greater and lesser omenta were sutured to the anterior surface of the stomach. The abdomen was then closed using chromic catgut No. 000 for the peritoneum, and interrupted cotton sutures for the fascia and for the skin. The patient was given 500 c.c. whole blood on the operating table. Convalescence was excellent and the patient was given a high protein, 4,000 calorie diet on the first postoperative day. Sutures were out on the ninth day. He was scheduled for the second stage of the operation on Oct. 20, 1944, but this had to be canceled because of an upper respiratory infection.

On Oct. 27, 1944, through a ninth intercostal space incision a total transthoracic gastrectomy was performed. Considerable difficulty was encountered separating the stomach from the pancreas but otherwise no special difficulties were experienced. About two and one-half inches of esophagus were removed with the stomach. An anastomosis was made between the jejunum and the esophagus in the chest cavity, using an inner row of continuous lock chromic catgut No. 000 and an outer row of interrupted quilting cotton. The Levin tube was threaded into the distal jejunal loop for feeding. The patient was given 2,500 c.c. of blood on the day of operation. The postoperative course was excellent. Tube feeding was started on the first postoperative day through the Levin tube that had been

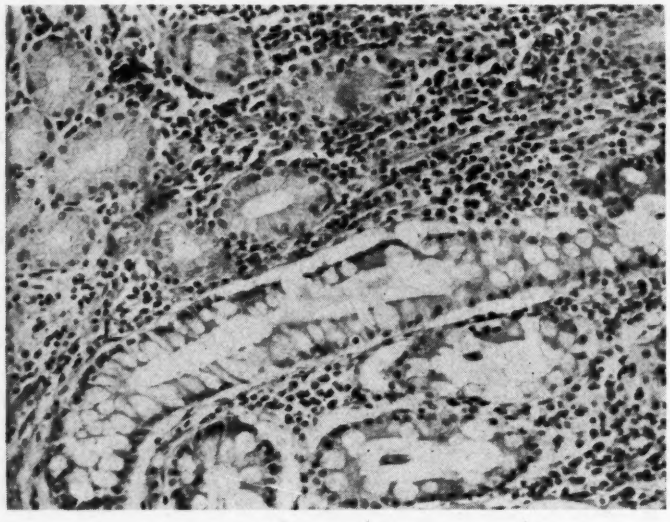

Fig. 4.—The third tumor in the body, showing junction of normal and malignant glandular tissue; note loss of differentiation in the malignant cells in the upper half of the section in contrast to the well-differentiated glandular cells below (×200).

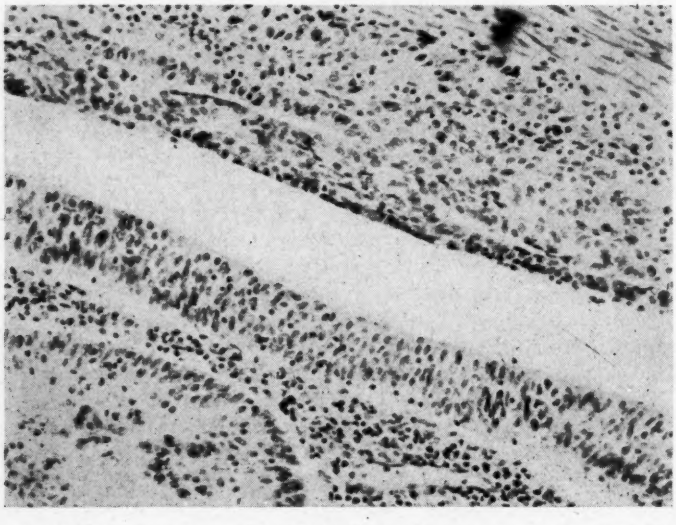

Fig. 5.—The fourth tumor in the body; note malignant cells infiltrating the submucosa and the malignant cells in this group smaller and more anaplastic than those of the other tumors in the body (×200).

placed in the distal jejunal loop. Oral feeding of a high caloric soft diet was started on the third postoperative day because the patient pulled out the jejunal tube. Nov. 3, 1944, he was given 500 c.c. of whole blood to correct the anemia. A wound infection was drained on November 7, and opened into the chest cavity on November 9. This wound continued

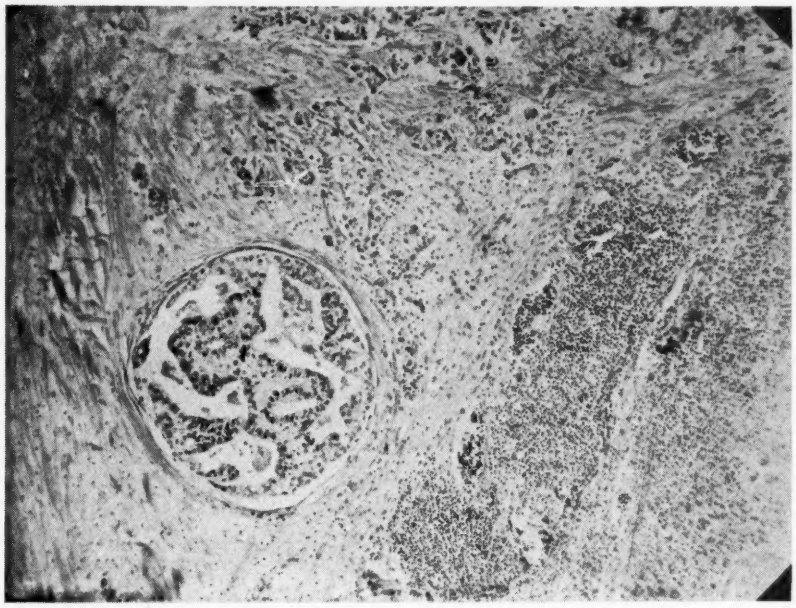

Fig. 6.—The fifth tumor, in the pylorus; note the malignant thrombus on the left side (×61).

Fig. 7.—A different magnification of the second tumor, showing large tortuous malignant glands (×61).

Fig. 8.—A different magnification of the fourth tumor in the body, showing junction of benign and malignant tissue with malignant infiltration of the submucosa (×61).

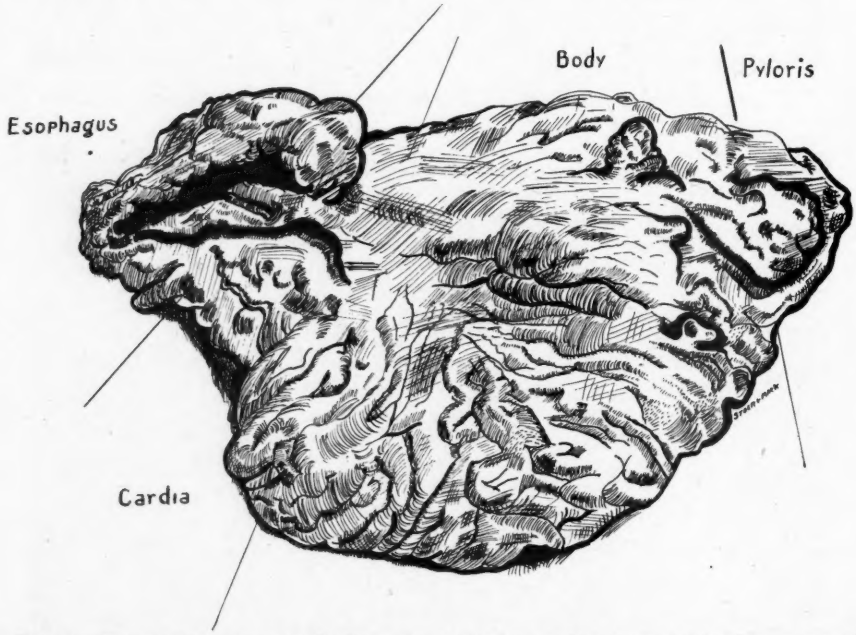

Fig. 9.—The stomach is opened along the posterior surface near to the lesser curvature. The normal esophageal mucous membrane is folded back and does not show well. The large tumor of the cardia can be seen extending into the esophagus. The deep ulceration in this tumor lies mainly in the esophagus. This tumor had metastasized to the lymph nodes of the lesser omentum; it involved all of the layers of the stomach wall. Three small pedunculated growths are present in the body. These were limited by the submucosa and did not invade the muscle. Although much alike microscopically, these tumors were separated by normal mucosa and submucosa. The papillomatous growth at the pyloris is 3 cm. in diameter at the base but also does not involve the muscularis. This is the tumor that was biopsied at the first operation.

to drain until December 6, at which time a large silk suture which had been used to approximate the ribs was extruded, after which the wound rapidly healed. Gastrointestinal series on November 28 showed no fistula and a large dilated upper jejunum which emptied rapidly. The patient was discharged on December 11 in good condition.

He took care of his farm until February 14, at which time distention began. His local physician cared for him at home until his death, Feb. 28, 1945, which was attributed to carcinoma of the rectum. No biopsy was taken and autopsy was not available. He did not return to the hospital after being discharged and the only follow-up was obtained through the local social service worker. It seems more logical to suspect that death was due to metastases from the large carcinoma of the cardia, rather than a new carcinoma of the rectum, as his rectum was negative to digital examination at this hospital.

Pathology Report.—The specimen consisted of 6 centimeters of esophagus, the entire stomach including the pylorus, the greater and lesser omenta, and lymph nodes. The stomach had been previously opened and measured open 15 by 18 cm. A portion of greater omentum measuring 10 by 6 cm. with a thickness of 1 cm. was attached to the greater curvature. It consisted of numerous lobules of fat in which no firm nodules could be felt. The serosa of the stomach was pale yellow, smooth, and showed a few petechiae. Toward the cardiac end the wall of the stomach was very firm, rigid, and hemorrhagic. It measured in its thickest portion 3.5 cm. and extended 4.5 cm. from the resected border. The lumen of the cardia measured 2 cm. in its narrowest portion. The mucosal surface of the cardia was very coarsely granular, yellowish red with an ulcer in the central portion measuring 1 by .05 cm. and approximately 0.3 cm. in depth. The base of the ulcer was yellow and soft. The edges were smooth yellowish red, firm and rounded. The fundus of the stomach was soft and covered with a hemorrhagic mucus. Extending from the lesser curvature to the greater curvature were four sessile, pedunculated masses. The largest was 3 cm. in diameter at the base. They involved the mucosa and the submucosa, but not the muscularis. They were pale yellow, smooth with a few small furrows but not ulcerated.

Microscopic Diagnosis.—(1) Four papillary adenocarcinomas of the mucosa of the stomach apparently arising from adenomatous polypi. (2) Ulcerating carcinoma of the cardiac end of the stomach infiltrating the muscularis, with metastases to the perigastric lymph nodes.

SUMMARY

A case is reported with five primary carcinomas of the stomach treated by transthoracic total gastrectomy. As far as I could determine this is the first reported case of this type. A radical total gastrectomy was successfully performed transthoracically, but the patient died suddenly three months later after a sudden onset of distention, which may have been due to metastases.

My thanks to Dr. Charles Dunlap of the Department of Pathology of Tulane University and Mr. William Stewart of the photographic department of the Louisiana State Medical School for their help and advice in preparing the photographs.

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EARLY DIAGNOSIS AND MANAGEMENT OF SMALL INTESTINAL OBSTRUCTION

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THE purpose of this discussion upon the early diagnosis and treatment of small intestinal obstruction is to emphasize the possibility of this condition in abdominal colic not localized to any quadrant or specific viscus in the abdomen.

Small bowel obstructions may be divided into those external, on the surface of the abdomen, and those hidden within the abdominal cavity.

Those on the surface of the abdomen are strangulated obstructions and are easily diagnosed. Rarely is there prolonged delay because the patient is aware that the long-existing hernia is no longer a symptomless affair but has suddenly become an irreducible mass, firm and hard. The abdominal pain and symptoms are associated with this persistent protrusion. The physician, more accustomed to recognize the significance of this clinical entity, promptly calls surgical consultation and operative intervention is instituted, usually before bowel gangrene intervenes.

We have not been sympathetic with attempted medical reduction of strangulated hernia. We know that, if successful, nothing permanent has been done to prevent its recurrence and that the viability of the reduced bowel is speculative. We know that it is better to reduce the bowel under direct vision, inspect it carefully for adequate circulation, and repair the hernial defect. Then, and only then, can one be certain of the viable continuity of the bowel and only then has anything been done to prevent a recurrence of the catastrophe. We, therefore, do not attempt manipulative reduction in strangulated hernia but advise immediate surgical repair.

Those obstructions within the abdomen are hidden from sight and the diagnosis is often delayed because the symptom complex is not appreciated by the attending physician. Delay in receiving medical attention is due to a belief by the patient that the abdominal pain is due to some insignificant cause. Often many harmful home remedies have been used. As the result of this delay and ill-advised treatment, serious complications often have developed. The situation is, therefore, frequently the result of delay of both patient and physician; consequently, when first seen the patient is in an advanced stage of small bowel obstruction, presenting distention, vomiting, and often peritonitis from bowel rupture.

The intra-abdominal small bowel obstruction may be a simple form of obstruction in which the viability of the bowel is not in jeopardy, or it may be a strangulated or volvulus type in which the blood supply is obstructed and

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gangrene is imminent. In the former, delay is not so serious and can be tolerated; in the latter, delay is serious and may mean the life or death of the patient.

The simple or nonstrangulated types of obstruction may result from bands of adhesion, angulation of the bowel by adhesive bands, or intrinsic lesions within the bowel, such as an obstructive gallstone or neoplasm. Immediate operation is not a problem in simple nonstrangulating obstruction. However, when the blood supply is damaged to a segment of small bowel, as happens in a strangulation, volvulus, or intussesception, it becomes of paramount importance and must be released at once, regardless of the physiologic resources of the patient, otherwise gangrene, rupture, and peritonitis will ensue. Here rehabilitation measures must, for the moment, be deferred in the interest of bowel viability. Thus the surgeon is faced with two problems in small bowel obstruction: First, a clear distinction must be made as to the probable nature of the obstruction. Second, the integrity of the blood supply to the bowel must be carefully considered.

There are some points of diagnostic importance which will aid in arriving at a rather accurate conclusion. In simple obstruction, rigidity and localized abdominal tenderness are not present. In loop obstruction where the bowel is strangulated by a loop of bowel either passing through a band of adhesion or becoming twisted upon itself in the nature of a volvulus, there is localized abdominal tenderness and some rigidity, as the distended loop of bowel contacts the parietal peritoneum. This is likewise true in intussusception of the terminal ileum into the ascending colon and to some extent with bands of adhesions to the anterior parietal peritoneum obstructing the bowel. When localized tenderness and rigidity are present in small bowel obstruction it may be stated that a strangulated loop of bowel is present and the blood supply is in danger.

While intestinal obstruction presents few or no early physical signs, their very absence indicates that there is no localized inflammatory process in any of the four quadrants of the abdomen. The colic is diffuse and periodic and differs from any other form of abdominal colic, which is usually localized in character and constant in type. The signs of a localized process are not present, as in acute inflammation of the appendix or gall bladder, or a perforated duodenal ulcer. The pain in obstruction comes in paroxysms, with intervals of relief. Peristalsis may be seen over the abdomen during the spasms of pain, and auscultation may reveal the increased sound of intestinal contractions. The abdomen presents a noisy rumbling sound during these paroxysms—borborygmus.

It must be remembered, as emphasized by Wangensteen and Goehl, that the passage of gas or movement of the bowels does not eliminate the possibility of obstruction. The bowel distal to the obstruction is unimpaired and may function normally, completely emptying itself of gas and feces. Wangensteen and Goehl stated that good results may be obtained by an enema, and unless this is kept in mind, a false security may result from a copious passage of gas or evacuation of the bowels.

Vomiting is dependent upon the duration and the level of the obstruction.

The very absence of early physical signs suggests the possibility of bowel obstruction and, in a patient who has had one or more abdominal operations, should bring to the surgeon's mind the possibility of an adhesive obstruction and cause him to seek the information which the radiologist can so accurately furnish.

The typical transverse pattern, described by Case, is not necessary for a diagnosis of small bowel obstruction. Collection of gas in the small bowel in the adult may be considered as synonymous with obstruction. In very small children, gas may be seen in the small bowel and be of no diagnostic significance. The presence of gas after obstruction is not a late development; it is seen early after the onset of the obstruction, usually being demonstrable without difficulty in four or five hours. The distribution of the gas in the small intestine is indicative of the probable type of lesion. Again let me emphasize that in simple obstruction it may be centrally located, with a transverse long axis, while in loop obstruction the dilated loops may assume no definite pattern, and proximal bowel distention is slow in developing. If the walls separating loops are thick, it signifies the presence of fluid or exudate. Gas in the large intestine is quite in contrast to gas in the small bowel, in that the long axis is vertical, the bowel wall is thicker, and haustral markings are present. The stepladder appearance of small bowel distention indicates advanced obstruction and is associated with a variable degree of abdominal distention. The gas is present and can be demonstrated long before distention and this particular pattern has developed. Thus, it may be said fairly accurately that the x-ray can make an early diagnosis of small bowel obstruction and that it can demonstrate the distribution of gas, and the location and probable nature of the obstruction.

From an abdominal roentgenogram, one can readily determine whether the distention is in the large bowel or the small bowel. If it is in the large bowel, it is usually a closed loop obstruction; the ileocecal valve prevents regurgitation into the ileum. If it is in the small bowel, the type and character of the distention depend upon the nature of the obstruction, and from the pattern of bowel distention the urgency of the situation becomes apparent.

In postoperative distention there may be a question as to whether a mechanical obstruction is present or a paralytic ileus. In the former event, the small intestines are distended, while in the latter there is distention of both the small and large bowel. A radiographic film shows the nature of the gaseous distention and helps to distinguish between the two conditions. If the obstruction involves the small bowel, it is distended and the colon is empty; in ileus, gaseous distention is present in both the small and the large bowel. Repeated films may be necessary to determine the certainty of an ileus. Consideration must also be given to the presence of a so-called silent and painless abdomen as a differential point in diagnosis.

A simple adhesive band producing proximal distention of the bowel results in no immediate vascular damage, and operation may be deferred until rehabilitation of the patient can be accomplished and intestinal decompression

established. A loop obstruction, volvulus or strangulation, on the other hand, demands immediate operative interference because of the danger of devitalization and bowel gangrene. With such an obstruction, the bowel is not observed assuming the transverse position but forming one or more distended loops, with no set pattern and with little or no proximal distention until the obstruction has been present for some time. The reason for the delay in distention of the proximal bowel is not understood, but it is probably due to the associated hyperemia and edema. Wangensteen and Lunch mentioned the altered state of the bowel proximal to the infarcted loop as a partial explanation.

The simple adhesive obstructions are the most common types involving the small intestine, and their presence can be detected early by radiologic study. The pattern is characteristic, and the sequelae of loss of electrolytes, of body fluids and distention are in relation to the extent and level of the obstruction.

CASE 1.—M. I. entered the hospital with abdominal pain, periodic in character, and with moderate distention. Little or no fluid loss from vomiting had occurred. A recent operation had been performed elsewhere for an acute appendicitis. Recovery had been uneventful, without protracted hospitalization or abdominal drainage.

Obstruction was suspected because of the nature of the complaints, the absence of symptoms indicating any other type of colic or localized inflammatory process, and the presence of an abdominal operative scar, which always adds weight to the suspicion of small intestinal obstruction. An x-ray picture (Fig. 1) revealed obstruction of the distal portion of the small bowel with only moderate proximal bowel distention. Favorable systemic and local conditions warranted immediate operation, which corroborated the x-ray diagnosis of small bowel adhesive obstruction. The terminal ileum was constricted and angulated by a band of adhesion. Recovery was uneventful.

CASE 2.—A similar condition is shown in M. H., a girl of 13 years who, six weeks previously, had an appendectomy for acute appendicitis, accompanied by drainage. Abdominal pain suggestive of obstruction prompted an x-ray study of the gaseous distribution in the intestinal tract. This readily revealed a simple obstructive lesion of the terminal small bowel (Fig. 2). Again operation corroborated the x-ray diagnosis. Recovery was prompt after an adhesive obstruction six or eight inches from the cecum was freed.

Loop obstruction presents an entirely different radiographic pattern and a distinct surgical urgency because of impending bowel gangrene.

CASE 3.—Fig. 3 shows the pattern of intestinal gas in a middle-aged woman, S. B., who had previously had a total hysterectomy for a fundal carcinoma of the uterus. The x-ray diagnosis was a loop obstruction of the small intestine, without proximal bowel distention, and immediate operation was advised. The possibility that obstruction was due to metastatic cancer was considered. At operation a loop obstruction with volvulus and gangrenous bowel, adhesive and benign in character, was found. Resection with side-to-side anastomosis was followed by normal convalescence. The clinical symptoms and radiologic film indicated a loop obstruction, which demanded immediate operation. The operative findings confirmed this conclusion. The resected specimen is shown in Fig. 4.

Small bowel obstructions frequently occur in association with inflammatory lesions within the abdomen and usually present the characteristic pattern of a progressive proximal bowel distention in which the viability of the bowel is not in jeopardy. In this type of obstruction it is not often necessary to interfere surgically, as the condition results from localized inflammation and edema which

narrow and constrict the adherent bowel to the point of obstruction, often in many places. The obstruction will usually disappear and the bowel again become patent, if the patient can be carried along by intestinal intubation and such rehabilitation methods as administration of fluids, saline solution, and transfusions until the inflammatory process has subsided.

Surgery is attended by great danger to the inflamed edematous bowel and may lead to extension of the infection. Intestinal decompression by the Miller-Abbott tube reduces distention and lessens the edema and hypertrophy proximal

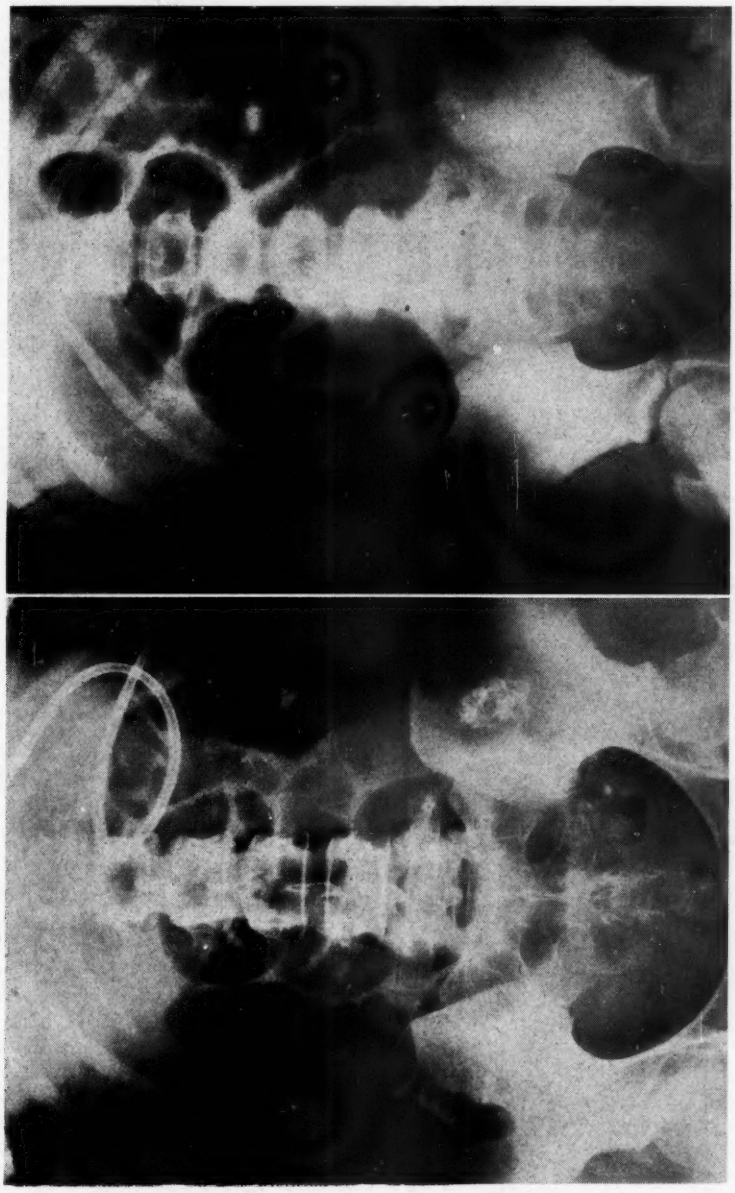

Fig. 1 (Case 1).—Early small bowel obstruction from postoperative adhesive band. Note transverse position of small bowel, distended coils, and gas seen in the right colon; rapid recovery followed operation.

Fig. 2 (Case 2).—Early small bowel distention assuring transverse position. This is adhesive band type obstruction; recovery followed operation.

to the obstruction. With intubation and appropriate systemic measures, recovery will occur without surgery being resorted to. Enterostomy is not required, as a more effective decompression measure is found in intestinal intubation. Enterostomy is ineffective, since it drains only a limited segment of the bowel or a few distended loops and has many hazards.

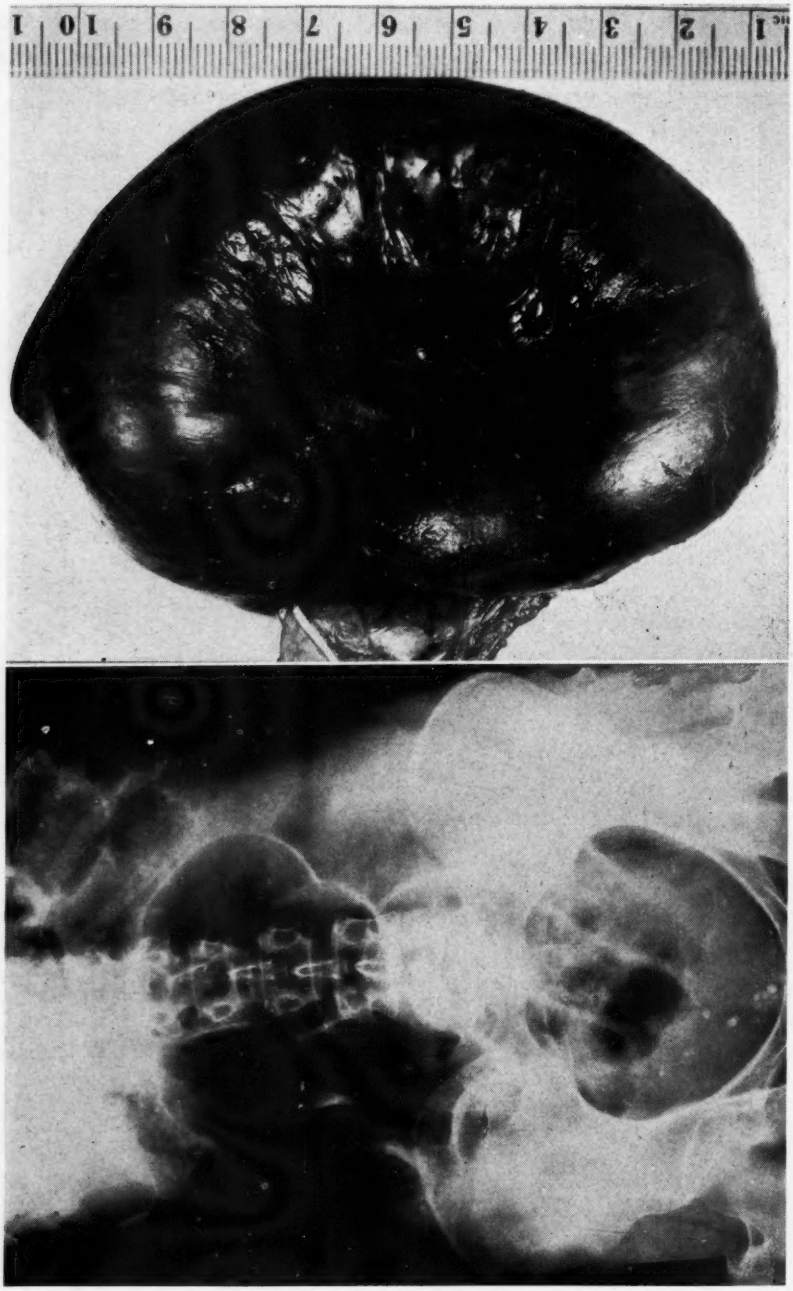

Fig. 3 (Case 3).—Note distended loop small bowel not assuming transverse position, distended without definite pattern, characteristic of loop obstruction or volvulus.
Fig. 4 (Case 3).—Specimen of gangrenous small bowel obtained at operation, resection and bowel anastomosis recovered.

CASE 4.—This case illustrates the value of conservative decompressive measures. W. H., a 16-year-old boy, presented the picture of an acute abdominal condition of several days' duration. The abdomen was boardlike but not distended; the pulse was fast, the temperature was elevated 3½ degrees, and the white blood count was 20,000. The patient was dehydrated and in very unfavorable condition for immediate surgery. An x-ray film showed no evidence of a pneumoperitoneum. Because it had been several days since the onset of the acute process, and because of the poor condition of the patient, conservative measures were adopted. A mass developed and subsequently a large appendical abscess was surgically drained and the appendix removed. Convalescence was stormy but progressive until the nineteenth postoperative day, when abdominal pain, periodic and cramplike in character, developed. Diffuse abdominal colic was followed by vomiting. Obstruction was suspected, and a roentgenogram of the abdomen (Fig. 5) showed rather extensive distention of the small bowel. A diagnosis of an inflammatory obstruction of the small intestines was made. The use of the Miller-Abbott tube (Fig. 6), adequate fluids, saline solution, glucose, and blood transfusions resulted in complete recovery after a secondary abscess spontaneously drained through the operative incision. After forty days of hospitalization, convalescence was complete and the patient was discharged.

In patients of advanced years in the absence of previous abdominal surgery, the possibility of a colonic lesion must be given careful consideration. This can be most effectively determined by barium enema. Such a lesion being excluded, some variety of small bowel obstruction must be considered. In Case 5, a barium enema excluded a colonic lesion.

CASE 5.—A man, aged 73 years, presented a three-day history of very slight abdominal pain and progressive abdominal distention. There had been no vomiting. There was increasing difficulty in bowel evacuation and none had occurred for five days. No operative abdominal incisions were present. An x-ray view of the abdomen showed small bowel distention (Fig. 7) and some excess amount of gas in the colon. A barium enema showed no colonic obstruction. A Miller-Abbott tube was passed successfully and the small bowel deflated (Fig. 8). A mass developed in the right iliac fossa and at operation a gangrenous appendix with abscess was found. Recovery was uneventful.

Mesenteric thrombosis is in reality an obstruction since peristalsis is abolished and bowel gangrene is imminent. The symptoms are different, as acute sudden pain may usher in the catastrophe. The x-ray picture shows gaseous distribution in the small bowel tract. With sudden onset, continuation of the pain and a gaseous distribution in the small intestines, abdominal exploration should be done. Segmental resection may be possible but too often the entire supply of the superior mesenteric artery is involved and nothing can be done.

CASE 6.—Mrs. H., ten days following thyroidectomy for long-standing hyperthyroidism and mild cardiac decompensation, on the eve of her departure from the hospital, was suddenly seized with severe persistent pain in the abdomen. An x-ray picture of the abdomen showed small bowel accumulation of gas. A tentative diagnosis of mesenteric thrombosis was made and abdominal exploration was done. The entire small bowel and the entire right colon were black. Subsequently at autopsy, a thrombus was found plugging the superior mesenteric artery. Nothing was found in the heart and no arterial sclerosis or atheroma was found in the arterial tree. The origin is unknown. Figs. 9 and 10 show the distention of the small intestines and the autopsy specimen of the involved segment of the superior mesenteric artery.

Intussusception presents two avenues for profitable use of the x-ray. First, it is most valuable in confirming the diagnosis suspected from the passage of

blood and mucus in the stools of an infant or small child who has abdominal colic and a palpable mass. Second, it is the only guide by which one may be certain of reduction by nonsurgical means. Only with the aid of a thin opaque enema can complete reduction be determined. Reduction may appear to be successful when in reality a segment at the ileum may remain intussuscepted. The completeness of reduction can be determined only by use of an opaque medium which shows the entire outline of the colon and cecum.

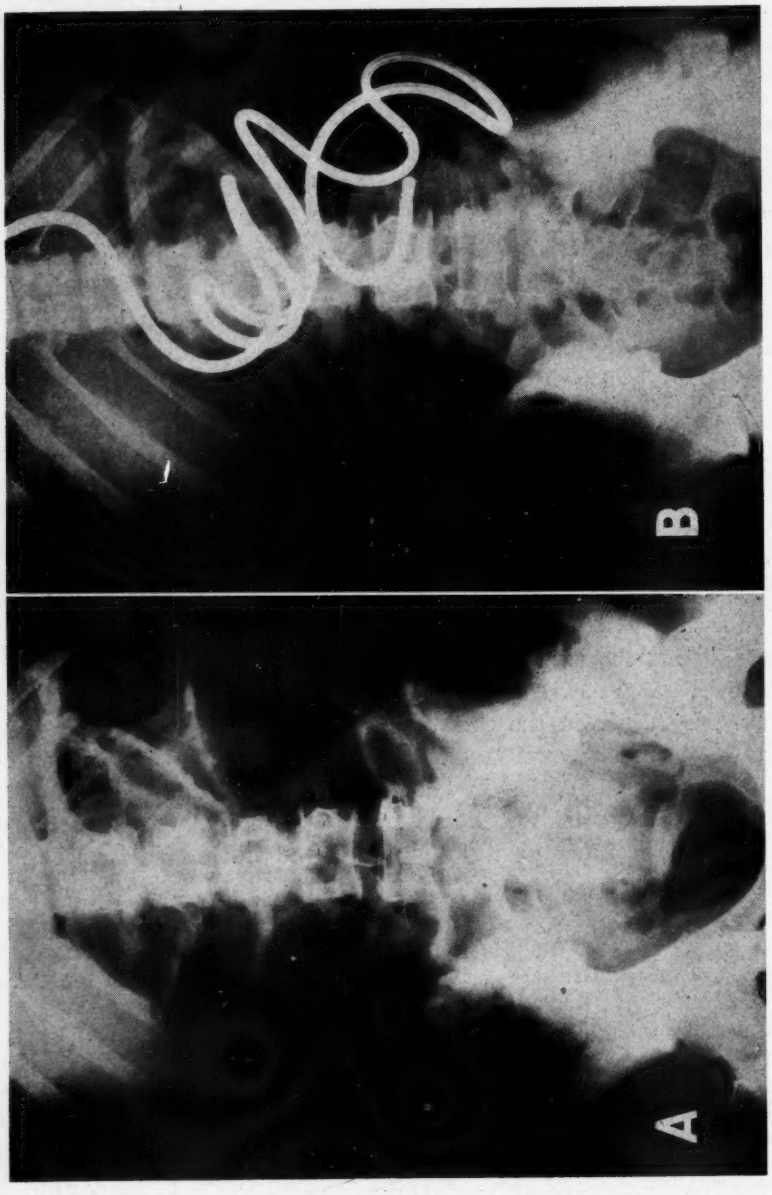

Fig. 5 (Case 4).—Small bowel obstruction following drainage of appendical abscess. Secondary abscess resulted in obstruction; recovery took place when abscess spontaneously drained through operative incision.

Fig. 6 (Case 4).—Small bowel intubation by Miller-Abbott tube; nonoperative recovery.

Fig. 11 shows an intussusception completely reduced by barium enema as demonstrated by a well-visualized cecum. Fig. 12 shows an intussusception of the ileum into the splenic flexure, requiring surgical reduction.

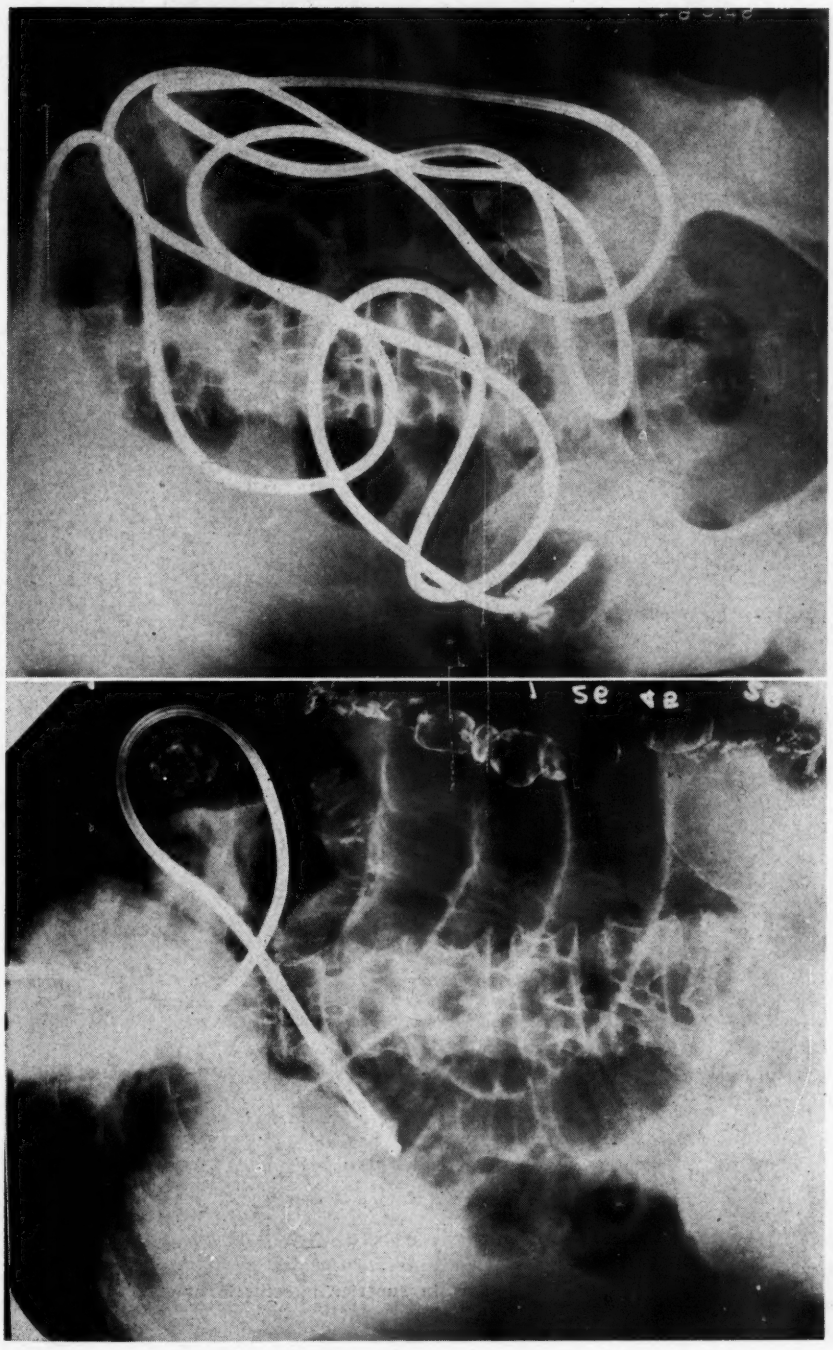

Fig. 7 (Case 5).—Note the intestinal pattern in which coils of dilated small bowel assume the transverse position; there is some excess amount of gas in the colon and an ilius due to acute appendicitis.
Fig. 8 (Case 5).—The Miller-Abbott tube is shown well down in the bowel tract with resulting decompression.

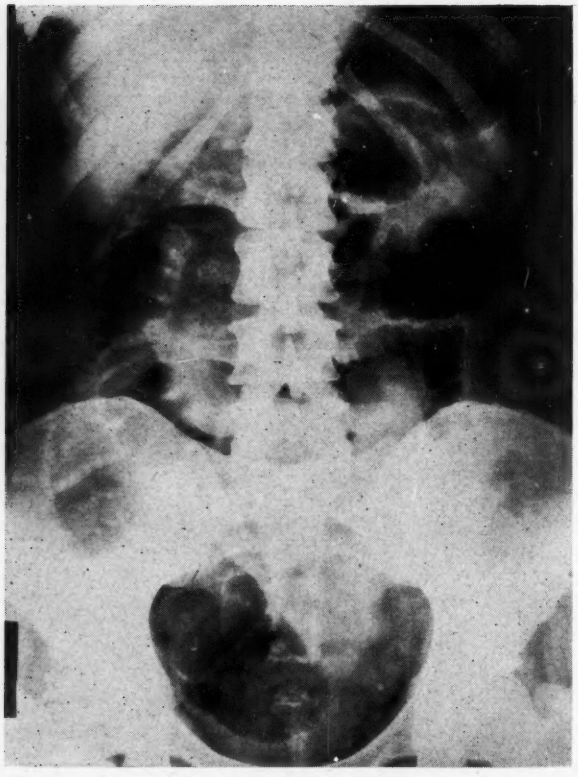

Fig. 9 (Case 6).—Small bowel distention from mesenteric thrombosis.

Fig. 10 (Case 6).—Thrombus in superior mesenteric artery.

Intrinsic lesions obstructing the small bowel are due to the occasional obstruction from a gallstone or incomplete obstruction from a neoplastic lesion. The symptoms are those of biliary colic with subsequent bowel obstruction or progressive abdominal distress from a gradual occlusion of the lumen by the neoplastic growth.

Surgical management of stone obstruction depends upon the local condition of the obstructed bowel. If the stone can be dislodged it should be pushed upward to an uninvolved area of the bowel and removed through a longitudinal incision which is closed transversely. If edema and reaction prevent dislodgment of the stone, resection with anastomosis is advisable. Incisional removal through an indurated edematous bowel is hazardous. It will not heal.

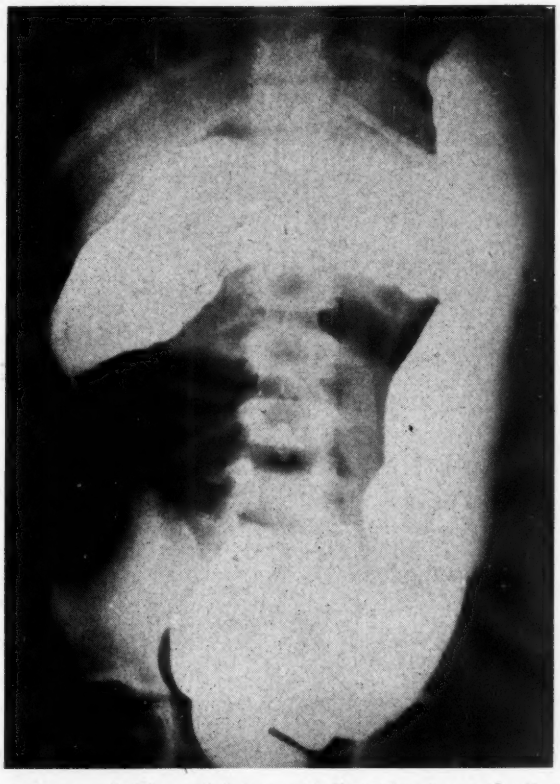

Fig. 11.—Barium enema reduction of intussusception showing reduction to be complete.

Neoplastic lesions require resection when possible. If inoperable, anastomosis should be made between the proximal and distal limbs of the bowel around the lesion.

In partial obstruction much difficulty may be experienced in making a diagnosis from the radiographic film unless intermittent complete obstruction is present. Lockwood emphasized the advantage of opaque medium as an aid to diagnosis. Its significance centers around the rapidity of its progress through the intestinal tract. Any retardation of the barium or the detection of a mal-

formed loop is of great significance. Frequent roentgenograms are necessary to follow the barium in its intestinal advance.

INTESTINAL INTUBATION

The indications for the use of the Miller-Abbott tube in small intestinal obstruction are very definite. In the Research Hospital the procedure of passing the tube* is the function of the radiological department.

The tube is indicated in simple adhesive obstruction with extensive proximal distention. It is valuable in early obstruction of a similar nature to prevent postoperative ileus and to hasten restoration of an already partially distended bowel. It is contraindicated as a preoperative measure in loop obstruction, in volvulus, or in strangulated obstruction where the viability of the bowel is in jeopardy. It may be valuable as a postoperative agent to prevent further distention and to hasten restoration of bowel tone.

Fig. 12.—Extensive intussusception of small bowel well into colon, not reducible by barium enema.

Although the Miller-Abbott tube has fallen into disrepute in many sections of the country, it is felt to be beneficial and can be applied in selected cases of intestinal obstruction.

The passage of the Miller-Abbott tube into the small bowel requires patience, along with a certain amount of skill. Much time can be saved by start-

*Successfully accomplished by the radiologist, Dr. Ira H. Lockwood, and his associates, whose splendid cooperation is here acknowledged.

ing the intubation under fluoroscopic control. The procedure followed by Lockwood is as follows:

The patient is brought to the x-ray department with the necessary equipment. The tube is assembled and checked by the radiologist. If the patient is apprehensive, gags easily, or is restless, he is given sodium phenobarbital (1 to 4 gr. intravenously, depending upon his size) along with atropine (1/150 to 1/75 gr.). The depressant action of the phenobarbital on the gastrointestinal tract is felt to be much less than with opiates.

The tube is inserted into the stomach through the nose and pushed down along the greater curvature in an attempt to pass it through the pylorus. If the tube does not enter the duodenum immediately, the balloon of the tube is inflated slightly and is left in proximity to the duodenum. Peristaltic action of the stomach will guide the tube into the small bowel.

In patients with paralytic ileus and in moribund patients the instillation of hypertonic saline solution into the colon or an infusion of hypertonic saline solution into the vein will result in an increase in the peristaltic activity of the bowel. Only one word of caution—the reaction to the saline solution is sometimes violent. One must be sure that the tube is on its way down into the small bowel before the saline solution is administered, as perforation of the bowel may result without any means of decompression.

In this series of cases with the Miller-Abbott tube used as an adjunct in intestinal obstruction, a definite improvement was found in the condition of the patients in twelve to twenty-four hours.

In the past five years, forty-one patients have been operated upon for small bowel obstruction and several have been treated for obstruction due to an intra-abdominal inflammatory process and have recovered without operation.

Analysis of the forty-one operative cases was as follows:

29 small bowel obstructions from adhesive bands in which no resection was necessary

10 resections for devitalized bowel (no deaths)

2 cases of carcinoma of the small bowel, jejunum, and ileum, obstructive (operative recovery)

Three deaths occurred in this series:

1 postoperative intussusception (child, pneumonia)

1 postoperative secondary small bowel obstruction following cholecystectomy for stones; cause of death was intestinal obstruction, peritonitis

1 coronary thrombosis, following operation for small bowel adhesive obstruction

The Miller-Abbott tube was used in the nonsurgical treatment of those obstructions due to localized inflammatory processes. It was likewise used as an adjunct in more than one-half the operative cases, either as a preoperative or postoperative measure. Clinical and radiographic evidence of postoperative small bowel obstruction has frequently led to recovery by decompression with the Miller-Abbott tube without operation.

SUMMARY

Classification of small bowel obstructions into strangulated hernias and those hidden within the abdominal cavity is discussed.

There is a discussion of strangulated hernia and reasons for immediate operation.

A description is given of the types of intra-abdominal obstruction of the small intestines and the immediate and remote effects of each.

There is mention of the indications for immediate or delayed operation.

Symptoms and signs of small bowel obstruction as distinguished from localized colic or inflammatory disease are emphasized.

Value of x-ray pictures in the diagnosis of obstruction and determining the type of obstruction is explained.

Value of x-ray is differential diagnosis between ileus and mechanical obstruction is discussed.

Indications are given for medical treatment of some type of intestinal obstruction where inflammation and infection are factors.

The diagnostic and therapeutic value of the x-ray in intussusception is mentioned.

Intestinal intubation, its indications, method of passage, and value are discussed.

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FISSURES OF THE ARTICULAR CARTILAGE OF THE PATELLA

Occurrence in Multipartite Patella

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THIS paper is presented to demonstrate that trauma or unusual stress to the knee may not only produce cracks and fissures of the articular cartilage of the patella[1] but may also affect in a similar manner the articular cartilage covering the ossicles of anomalous (multipartite) patellae of adults from 18 to 35 years of age. The interest lies first in the fact that the symptoms and signs encountered in these instances simulate to a certain extent those found in subluxations or tears of the semilunar cartilages and second, that those with anomalous patellae make up a high percentage of these cases. Since the osseous portion underlying the damaged articular cartilage was not fractured as demonstrated by radiographic examinations, there has been a ready tendency to overlook damage to the articular cartilage in the differential diagnosis of trauma to the knee. It appears that early recognition of tears or fissures in the articular cartilage of the patella and also that of an anomalous patella will aid materially in the plan of therapy and in better evaluation of the prognosis. As soon as more attention was given to this condition, the lesion was diagnosed in fifty-eight patients within a period of ten months. Twenty-three patients, or approximately 40 per cent of these cases, complained of symptoms in the knee for the first time. The duration of these symptoms was from several days to two months. In the other thirty-five patients, or approximately 60 per cent of the cases, who had recurrent symptoms of two or more months' duration, surgical intervention was performed in eleven instances including one with a bipartite patella. This inspection confirmed the clinical impression of the existence of fissures or cracks in the articular cartilage of the central portion of the patella in ten cases and that of the anomalous ossicle in the eleventh case.

The pathologic alteration in the cartilage of the patella may be readily suspected by an analysis of the mode of injury. Any mild to severe sudden force that tends to abut the patella against the femur with the leg in extension or flexion either directly or by torsion may initiate a fissure in the articular cartilage of the patella and may, in addition, occasionally similarly affect that of the contiguous femoral condyle.*

Recurrent incomplete or complete subluxation of the patella either due to anomalies of the skeleton, laxity of the capsule or lateral ligaments, or muscle imbalance about the knee joint also predisposes to such changes in the articular cartilage of the patella. It is important to note that the articular cartilage of the patella is one of the thickest of the skeleton and is highly vulnerable to very mild direct or glancing blows. Furthermore, fissures may develop in the articular cartilage of the patella of certain young adults who have participated

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*According to Owre[2] the site of stresses and strains upon the articular surface of the patella varies in flexion and extension. In flexion it is the lateral facet, and in extension it is the medial facet, of the patella which bears the respective impacts of the femur.

in unusual long hikes, marches, mountain climbs, or long periods of physical exercise without incurring any single definite pronounced local trauma. Newly inducted members of the armed forces who undergo extensive physical training are especially susceptible to such damage to the articular cartilage of the patella.

In this paper an attempt will be made to answer the following questions.

1. What are the symptoms and signs of fissures of the articular cartilage of the patella?
2. What are the significant radiographic findings?
3. What is the treatment and prognosis in the acute and chronic or recurrent forms?
4. What are the gross and microscopic findings of the involved articular cartilage?

CLINICAL FINDINGS

Symptoms.—Soon after an injury to the knee or after an unusual physical exertion, the patient may complain of sharp pains, instability, temporary locking, enlargement of the knee region, and inability to bear weight. The pain may be localized to the medial or lateral aspects of the knee or about the patella. Several days after the initial injury, the pain may become circumscribed to the patellar area, and it may be of such severity that walking or squatting is performed with great difficulty. Occasionally a click or sandpaper-like grating sound or vibration emanating from the knee may be heard or felt by the patient as the leg is actively flexed or extended.

In those patients with recurrent complaints lasting for two or more months following one or repeated injuries to the patella, enlargement of the knee region, temporary "locking," local pain, and loud crepitations are the foremost symptoms. While a swelling (effusion) may exist approximately from seven to thirty days following an initial mild trauma, it may recur at frequent intervals for many years in the severe or chronic types. Patients with prolonged recurrent symptoms may walk with the affected leg in fixed complete extension or in slight flexion in order to avoid pain and grinding crepitations in the knee.

PHYSICAL FINDINGS

Shortly following an injury to the patellar region, the examination often reveals an intra-articular effusion and generalized tenderness about the knee. Several days later the tenderness usually becomes circumscribed to the region of the patella and the effusion diminishes in volume. Passive rocking or percussion of the patella produces a tender reaction. With the aid of a stethoscope which is placed over the patella, high pitched cracking sounds are heard during active flexion and extension of the leg. Crepitation may also be felt by the examining hand as the patella is pressed onto the femur and passively displaced in the horizontal planes *(contact test)*, or by active contraction of the quadriceps muscles with the leg in maximal extension. Pain is experienced during the latter procedure when mild manual resistance is applied to the superior pole of the patella *(resistance test)*. It is interesting to note that in several cases in which the finding of subpatellar crepitation was equivocal, accentuation of this

sensation could be produced by flexing the thigh at an angle of 90 degrees at the hip joint while actively flexing and extending the leg *(stretching test)*. During the painful stage, one often encountered temporary partial restriction of active and passive motion of the leg in both the range of flexion and extension, especially after a short period of weight-bearing. This finding may simulate that noted in a subluxed internal or external semilunar cartilage.

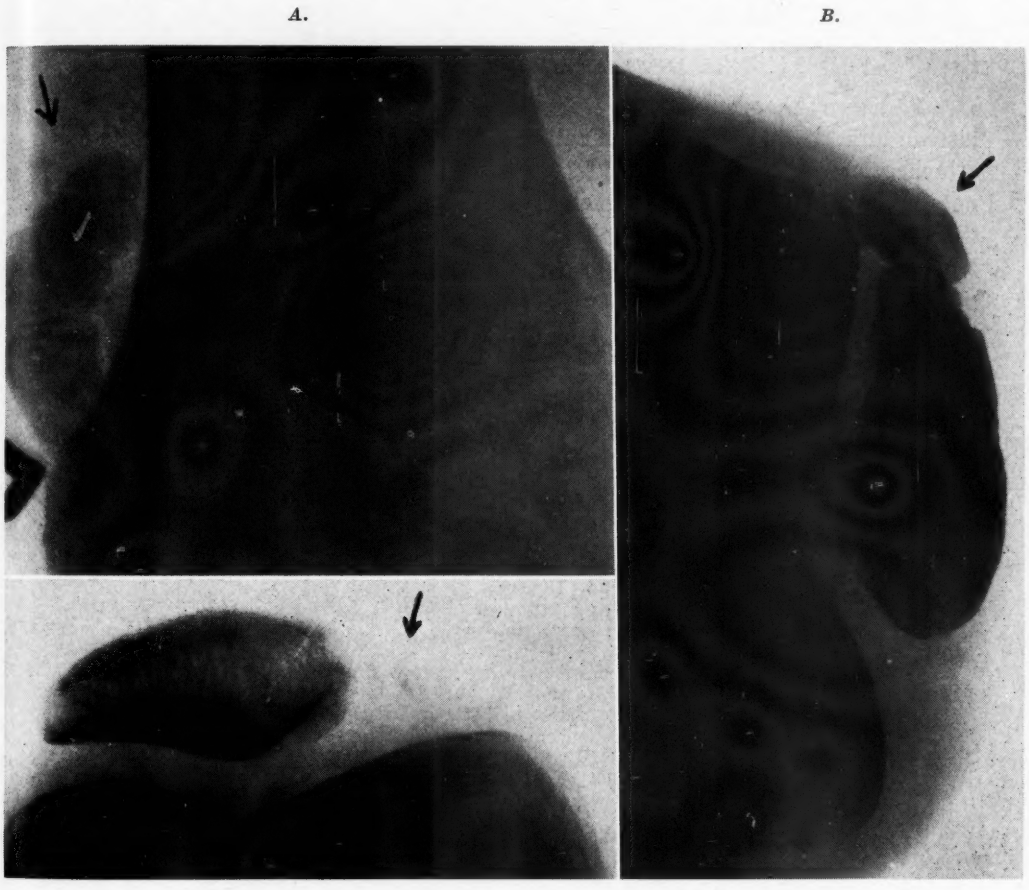


Fig. 1.—*A*, Note the three ossicles in the outer superior quadrant of the patella (quadpartite patella.) *B*, Note the projection of these ossicles into the articular cavity beyond the normal articular surface (quadpartite patella). *C*, Note the ossicles on the medial aspect of another patella (tripartite patella).

In those patients presenting a history of repeated injury to the patellar region, or those with long-standing symptoms following a single trauma to that site, examination revealed a definite thickening of the synovial tissues and frequently an increase in the volume of intraarticular fluid. Sometimes the pain over the patella was of such severity that the patient could not kneel and could walk only with his leg in fixed complete extension or in slight flexion. These objective findings were present in addition to the ones previously mentioned in the acute cases.

It should be stressed that fissures or cracks of the articular cartilage of the patella may be coexistent with tears of the internal or external semilunar cartilages or of the cruciate ligaments or relaxation of the posterior or lateral ligaments. When this occurs, additional signs such as tenderness over the lateral surfaces of the knee and instability of the tibia will be present which will mask to a certain extent those symptoms related to the damaged articular cartilage of the patella.

RADIOGRAPHIC FINDINGS

Radiographic examinations were made of both knees in the anteroposterior, lateral, and "jackknife" positions in each of the fifty-eight patients.[3] One may attach some importance to the fact that in this series of fifty-eight cases we noted eleven patients with anomalous patellae[4] (Fig. 1). The anomalies noted were that of ununited ossicles developed from accessory centers of ossification situated either in the outer superior quadrant or on the medial borders of the patellae.*

TABLE I

A. Bilateral Bipartite Patellae (5 cases)	
1 case, with acute symptoms	
4 cases, with chronic symptoms	
3 cases, each with symptoms in one knee	
2 cases, each with symptoms in both knees	
3 cases, with an ossicle in outer superior quadrant of each patella	
2 cases, with an ossicle on medial aspect of each patella	
B. Unilateral Bipartite Patellae (3 cases)	
1 case, with acute symptoms	
2 cases, with chronic symptoms	
3 cases, each with symptoms in the knee with anomaly	
2 cases, each with an ossicle in outer superior quadrant of one patella	
1 case, with an ossicle on medial aspect of one patella	
C. Unilateral Tripartite Patella (1 case)	
1 case, with chronic symptoms	
1 case, with symptoms in the knee with anomaly	
1 case, with ossicles in outer superior quadrant of one patella	
D. Bilateral Tripartite Patellae (1 case)	
1 case, with chronic symptoms	
1 case, with symptoms in one knee	
1 case, with ossicles on medial aspect of each patella	
E. Unilateral Quadpartite Patella (1 case)	
1 case, with acute symptoms	
1 case, with symptoms in the knee with anomaly	
1 case, with ossicles in outer superior quadrant of one patella	

*Surgical intervention in a case of bipartite patella of this series revealed the tears and cracks to exist in the cartilage of the ossicle and none in the articular cartilage of the body of the patella.

These patellae were in normal relationship to the femoral condyles in that they showed no evidence of fixed subluxation. Table I depicts some of the clinical and radiographic findings in the eleven cases of anomalous patellae.

Two other patients each of whom have had symptoms of pain, recurrent effusion, and crepitation for two years disclosed a circumscribed area of subchondral atrophy in the central portion of the patella of the affected knee. Otherwise the radiographic studies confirmed the clinical findings of increase in the volume of intra-articular fluid or thickening of the synovial tissues. No instances of osteochondritis dissecans, recent or old fractures of the body of the patella, postinfectious or infectious arthritis, or hypertrophic osteoarthritis were included in this series.*

DIFFERENTIAL DIAGNOSIS

Difficulty is encountered when one attempts to differentiate tears of the articular cartilage of the patella from those of the opposing cartilage of the femoral condyles. They are both treated in a similar manner.

Free intra-articular bodies, polypoid synovial or fat pad tumors about the patella, osteochondromatosis or villonodular formations of the synovial lining may also produce effusion, subpatellar crepitations, and temporary lockings. Palpation usually reveals the presence of one or more bodies, and radiographs frequently show soft tissue shadows, or calcified or ossified masses either in the joint cavity or in the capsular tissues of the knee.

Symptoms and signs caused by chronic infections such as tuberculosis of the synovial lining or of the bones in the knee joint may infrequently simulate the physical findings produced by tears of the articular cartilage of the patella. Examination of the guinea pig inoculated with the synovial fluid aspirated from the knee joint and the radiographic evidence of atrophy or destruction of the articular surfaces of the bones of the affected knee may aid in the differential diagnosis.

Occasionally, a completely dislodged torn internal semilunar cartilage lying in the intercondylar fossa may to a certain extent parallel the findings caused by a cracked articular cartilage of the patella. The history of repeated "lockings" of the knee, the presence of localized tenderness over the medial surface of the knee in the region of the semilunar cartilage, especially of the posterior horn, and the persistence of effusion in spite of complete bed rest should make one suspicious of a torn and displaced semilunar cartilage.

Osteoarthritis, tangential fracture, and osteochondritis dissecans of the patella can be differentiated in most instances by radiographic examinations.

*We did observe a patient who had suffered severe injury (fissure) to the articular cartilage of the patella several years before, who recently experienced a vertical undisplaced fracture through the body of the same patella. The radiographs revealed a fracture line but no other pertinent findings. The clinical course of this patient was striking and distinctly different from that of other patients with simple uncomplicated undisplaced fractures of the patella. Pain in the knee of the patient with the previous injury to the cartilage was severe for many weeks after the occurrence of the fracture and interfered with active and passive movements of the leg. This is in sharp contrast to a series of other patients with similar fractures without previous injury to the articular cartilage. Specifically a follow-up study of these patients with simple uncomplicated fractures of the patella six months after the injury showed absence of local pain and occasional presence of subpatellar crepitation on weight-bearing or on active repeated flexion or extension of the leg.

TREATMENT

Patients examined after an injury to the knee or after participation in strenuous exercises of the types previously mentioned are treated by rest in bed for periods ranging from one to two weeks. The affected knee is covered with ice bags for the first few days to relieve pain and swelling. Subsequently, any type of dry or moist heat may be substituted to relieve the spasm of the thigh or leg muscles. Frequently traction is applied to the leg in order to overcome the spasm of the hamstring muscles.

No attempt should be made to flex forcibly or extend the leg either actively or passively during the acute painful stage, a period which may last from one to seven days. Exercises consisting of mild rhythmical contraction of the quadriceps muscles with the leg in maximal extension, however, should be encouraged as soon as possible after the advent of the injury. After the third week, or sooner if local pain is absent, active flexion and extension "resistance"

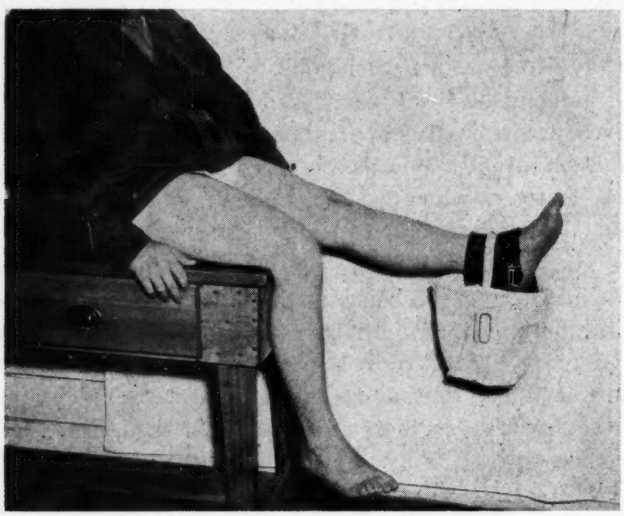


Fig. 2.—Note the method of actively exercising the quadriceps apparatus of the leg.

exercises* of the leg should be initiated and guardedly pursued. As soon as the power of the quadriceps muscles of the involved limb is approximately equivalent to that of the normal extremity, weight-bearing should be initiated. Special antilimping exercises as marching, walking, and dancing in cadence are stressed. No activities requiring excessive use of the knee should be encouraged, and only mild exercises should be pursued the first three or four months after the injury. We believe that graduated exercises to the quadriceps muscles will

*_Method._—The patient is seated on the side of the bed in an attitude permitting flexion and extension of the leg (Fig. 2). A sack containing a known amount of weight, usually a minimum of three pounds and a maximum of twenty pounds, is hung on the ankle of the involved limb. Exercises consisting of repeated flexion and extension of the involved leg are pursued for four fifteen-minute periods during the day. Similar exercises are followed on the normal lower extremity. Once a day the maximal quadriceps power of the lower extremities is tested by noting the number of minutes that each limb can sustain uninterruptedly a known weight in the position of extension without pain or fatigue. The aim of these exercises is to develop the power of the extensor apparatus of the affected limb to a level equaling that of the normal one.

abort rapid progression of the fissures and cracks of the articular cartilage of the patella and at the same time develop the muscle tone of the limb. In a majority of cases, limited activities for three or four months will restore the knee to a serviceable but not to a normal joint.

Immediate surgical intervention is not indicated in the treatment of primary acute mild tears of the articular cartilage of the patella. When, however, there is a tendency for subpatellar pain, effusion, and crepitation to recur frequently or when these symptoms persist for total periods longer than two months in spite of rest and limited activity, arthrotomy should be pursued.

When limited areas of the patellar cartilage are involved as was the case in nine of the eleven instances in our series, we removed the central area of fissured articular cartilage down to the subchondral bone and made small openings into the underlying subchondral bone marrow. Excessive amounts of articular cartilage should not be removed, neither should the infrapatellar fat pad or the synovial lining be resected at the same time. The removal of intraarticular free bodies or a torn or subluxated semilunar cartilage is however, not contraindicated. When the articular cartilage of the ossicle of an anomalous patella is involved, as was noted in one case, the underlying bone and cartilage of the ossicle were excised. For widespread cracked or split articular cartilage, removal of the entire patella is indicated. This was performed in a case of long-standing recurrent subluxation of the patella with marked secondary fissuring of the articular cartilage.[5]

Following an arthrotomy of the knee for the removal of fragments of torn articular cartilage, active contraction of the quadriceps muscles should be started soon after the surgical procedure. Moreover, the patient should attempt during the first fourteen days after the operation to elevate the entire limb without flexing the knee. These exercises strengthen the quadriceps muscles without imposing any unusual strain or irritation on the cartilage of the patella. Active flexion and extension and graduated "resistance" exercises of the quadriceps muscles should be initiated approximately fourteen days after the operation. The presence of pain in the patellar region is a contraindication for the continuation of flexion or extension exercises of the leg. Approximately six to eight weeks after the operation, or as soon as the quadriceps muscle power of the limbs is within normal limits, the patient should commence to bear weight and continue to do so if pain is minimal or absent. Activities which require excessive use of the knees should be restricted for a period of at least six months after the operation in order to permit the surgically produced defect in the articular cartilage to fill in with fibrous or fibrocartilaginous tissue.

When the patella is surgically removed, it is essential that active contraction of the quadriceps muscles be started soon after the operation. Active flexion and extension "resistance" exercises of the leg should be undertaken approximately seven days after the operation. Weight-bearing should not be stressed until the patient has accomplished almost full range of active flexion and extension of the leg without pain, and has almost fully developed the power of the quadriceps muscles.

Follow-up Examination and Prognosis.—In the acute cases including only those without previous involvement to the knees, the patients made an excellent recovery within two to three months after the initial trauma. These knees are for the most part highly susceptible to recurrence of symptoms and signs following very mild trauma or unusual exertion. Therefore, assignment to duty requiring excessive use of the knees should be avoided in view of possible recurrence of disturbance to the articulation.

In the chronic group there were seven patients in whom removal of torn and degenerated fragments of the articular cartilage of the patella was performed and there were two others in each of whom a torn internal semilunar cartilage was also removed. Follow-up examination of these nine patients six to eight months after the operation revealed free range of active and passive flexion and extension of the leg, loss of pain, absence of intra-articular effusion, and the presence of inconstant painless subpatellar crepitations. They were, however, unable to do very heavy duty without experiencing mild pains over the affected patella. Other patients with similar chronic disturbances in the patella whose onset of symptoms antedated entrance into the army were, depending on the severity of the symptoms and signs, either reclassified to perform sedentary duties or were separated from military service.

In the one patient (Case 10) in whom the ossicle and its cracked articular cartilage were removed from a bipartite patella, follow-up examination eight months after the operation revealed normal range of active and passive motion of the leg. The effusion and subpatellar crepitations which were noted prior to the operation were now absent. Yet in spite of good range of function the patient could not participate in strenuous activities for long periods as he experienced localized pains over the patella. He was permanently assigned to duty not requiring excessive or extensive use of the knees.

The excision of the patella in a case of recurrent subluxation of that bone with widespread fissures of the articular cartilage resulted in immediate loss of subpatellar pain and crepitation (Case 11). Follow-up examination six months after the operation revealed normal range of motion at the affected knee joint. Nevertheless, the patient had local discomfort after long hikes or mountain climbs. Therefore, he was assigned to duties limiting such strenuous activities.

PATHOLOGY

Gross description.—Surgical intervention in *eleven* cases gave us an opportunity to inspect the articular cartilage of the patella and the other structures in eleven knee joints. Except for the case of the bipartite patella, the central portion of the articular surface of each of the patellae, namely the medial facet and contiguous lateral facet, in an area approximately the size of a dime to a nickel was the site of the involvement. Here were numerous superficial or deep clefts, usually in a stellate design, which set off or enclosed one or more segments of shaggy yellow-white articular cartilage. In addition, flakes of cartilage loosely attached to the articular surface of the patella were noted in the vicinity of these fissures. The affected articular cartilage seemed to be easily separated

from the subchondral bone and was unusually fluctuant on pressure. Some of the detached flakes of cartilage were floating about in the synovial fluid or were embedded in the slightly reddened synovial tissues.

In the case of the bipartite patella, only the cartilage of the ossicle displayed a velvety shaggy yellowish-white surface with few superficial and deep fissures while that of the body of the patella presented no abnormal findings.

The patella, which was removed because of recurrent luxation, revealed on examination that its entire central portion measuring approximately the size of a nickel was the seat of deep stellate-shaped fissures (Fig. 3). Some of these clefts extended halfway into the depth of the cartilage and encompassed closely-set bundles of exposed fibrillar tufts.

In all eleven instances, one observed an edematous synovial lining in the knee and pannus formation over the periphery of the articular cartilage of the patella.

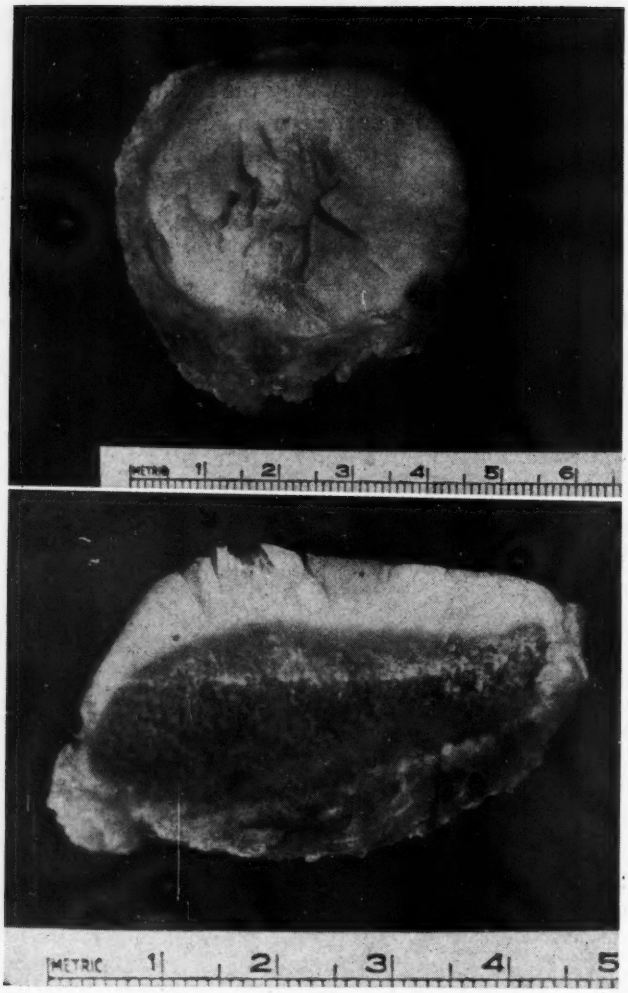
Microscopic Findings.—The striking feature was the partial loss of hyalin matrix, the secondary unmasking of the fibrils, and the presence of superficial and deep fissures in the articular cartilage. These abnormalities were especially prominent in the outer or tangential layer, and to a lesser extent in the contiguous zones of the articular cartilage. The flat cells normally situated in the outer or tangential layer were either absent or replaced by groups or nests of actively growing elliptical-shaped cells resembling those noted in fibrocartilage. Similar shaped cells, some filled with large amounts of chromatin, were also present in the depths of the cartilage especially adjacent to these abnormal fissures.

Evidence of partial repair as exemplified by the proliferating young cells on the articular surface and on the walls of the fissures was noted in the submitted portions of pathologic articular cartilage removed from the central portion of the patella. It appears that this meager attempt of healing of the cartilage was aided by the contiguous synovial fluid without benefit of granulation tissue.

In the case of the bipartite patella, the articular cartilage of the ossicle was markedly degenerated showing partial loss of matrix, unmasking of the fibrils, and poor staining of the nuclei of the original cells. At the periphery of the ossicle was a thick layer of vascular fibrous tissue which bound it to the body of the patella. Some of these blood vessels invaded the rim of the articular cartilage of the ossicle but no other reparative processes were in evidence. The bone in the removed ossicle was for the most part necrotic and was slowly being replaced by living osseous tissue. There was very little active hematopoetic tissue in the marrow spaces in the ossicle.

The findings of the microscopic examination of the central fissured portion of the articular cartilage of the surgically removed patella were similar to those observed in the submitted pieces of cartilage from the previously mentioned cases. In spite of the protracted period of irritation to the patella caused by recurrent subluxation, there was no evidence of sclerosis or fibrosis of the subchondral zone.

A.



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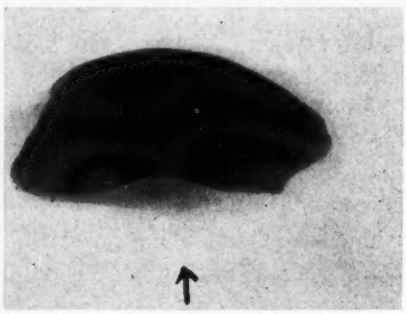


C.

Fig. 3.—*A*, Patella surgically removed because of recurrent subluxations; note the fissures in the articular cartilage. *B*, Section of the articular cartilage of this patella reveals fissures and tufts. *C*, Lateral view radiograph of this patella; note the frayed articular cartilage.

DISCUSSION

In order to comprehend the basis for the vulnerability of the articular cartilage of the patella, it is important to review briefly its histology and physical properties.

The articular cartilage of the patella of a young adult measures approximately from 4 to 6 mm. in height and is one of the thickest of the skeleton. It is relatively thickest in the central portion of the patella where the subchondral bone is slightly concave (Fig. 4). The articular surface is smooth, shiny, white, and fairly firm to the touch. On closer examination of the articular surface, one may discern without the aid of any magnifying lense, very fine grooves which extend from the superior to the inferior pole regions of the patella. These narrow shallow furrows are the result of the repetitive rotations of the femoral condyles on the patella.

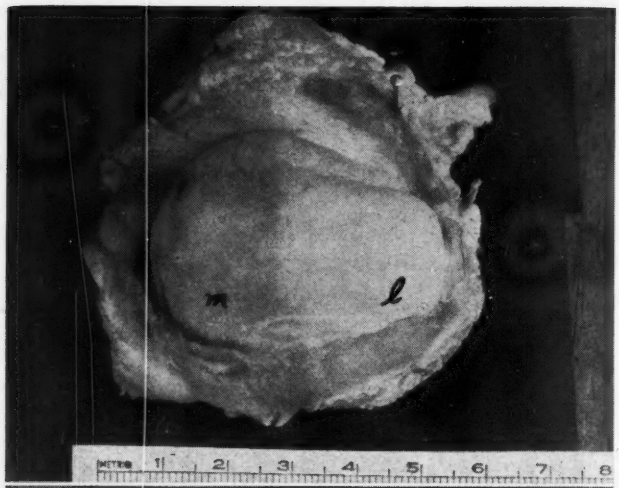
Normal articular cartilage is composed of cells and of very fine fibrils and interfibrillar hyalin matrix in such proportions that the fibrils are not clearly seen in the hematoxylin and eosin stained histologic preparations, but are observed microscopically with polarized light.* These fibrils which form a network for the envelopment of the matrix follow more or less a fixed pattern (Fig. 5). They commence from the calcified or deeper portions of the matrix and extend in a vertical fashion through the columnar and transition zones to the superficial layers and curve to lie parallel to the articular plane to form the outer articular or tangential horizontal layer. These fibrils finally take another vertical course through the transitional and columnar layers and attach themselves to the calcified matrix or they may continue in the horizontal plane and terminate at the region of the capsule-periosteum reflection at the periphery of the cartilage.[6] The massing of these looped fibrils as they traverse the surface of the cartilage to return to the calcified matrix zone results in patterns[7] which are specific for the articular surface of each bone (Fig. 6).

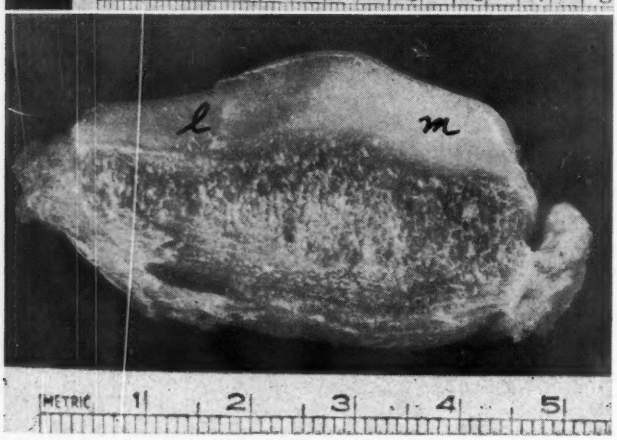
In addition to the system of vertical fibrils one finds another set which encircles the nests of cells in the columnar layer. These circular fibrils act as shock absorbers by virtue of their possession of elasticity and compressibility.

As far as the cells are concerned, they are usually flat or elliptical in the outermost or tangential layer and almost resemble in shape those present in perichondrium. In the contiguous transition zone, the cells are somewhat more spherical or elliptical than those in the tangential layer. The outlines of the spherical cells may be slightly distorted by the contiguous fibrils which are in an oblique course en route to the superficial tangential layer. In the columnar layer, one notes the presence of nests of spherical cells in its proximal portion and columns of cells in its deeper segment. These columns of cells may extend into the calcified portion of the matrix.[8] Here, most of the cells appear necrotic as evidenced by poor staining of their nuclei and cytoplasm. Furthermore, it is of interest that the forementioned constituents of the articular cartilage do not

*Normal articular cartilage is made up of the following four segments: (*A*) Thin outer tangential layer, flat cells and compact horizontal fibrils (Fig. 5); (*B*) thin transitional layer, elliptical cells and oblique fibrils; (*C*) thick columnar layer, nests and columns of cells, vertical and circular fibrils; (*D*) calcified matrix layer, columns of cells and vertical fibrils.

A.





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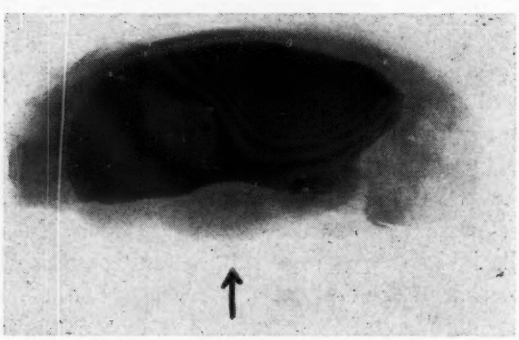

C.

Fig. 4.—*A*, Note the articular cartilage and the lateral (*l.*) and medial (*m.*) facets of a normal patella (post-mortem specimen). *B*, Section of the articular cartilage of this patella reveals its smooth glistening surface. *C*, Lateral view radiograph of this patella; note the thick articular cartilage and the concave subchondral bone.

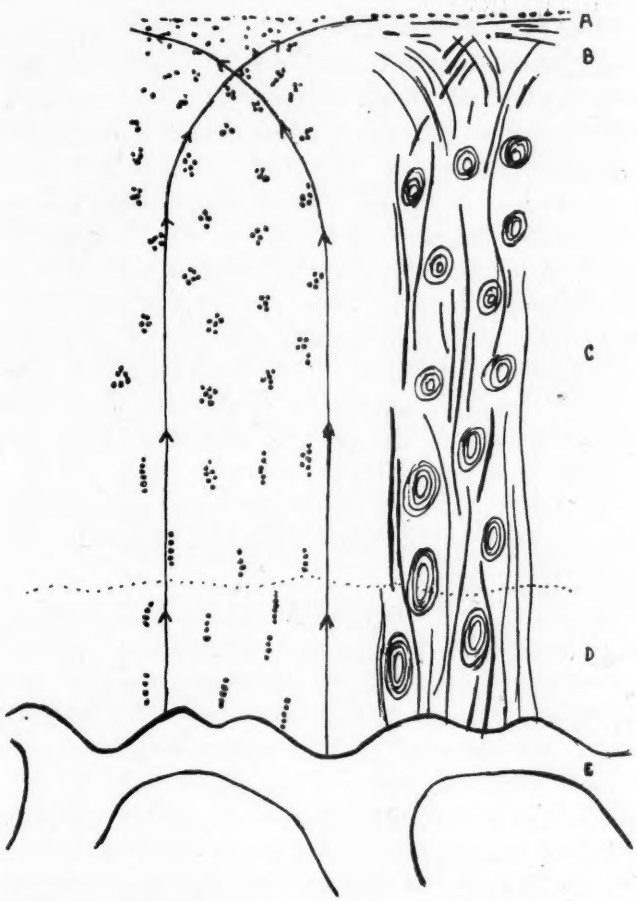

Fig. 5.—Diagram (after Policard[8]) to show the arrangement of the cells and the course of the fibrils in the articular cartilage as viewed microscopically. The arrows on the fibrils show approximately their course. *E* is the subchondral bone. See footnote in text (page 261) for explanation of the various segments of the articular cartilage.

Fig. 6.—Diagram (after Hultkrantz[7]) to show the general direction of the bundles of fibers on the surface of the articular cartilage of the patella as seen macroscopically.

cross into the subchondral region but make only direct contact with the dentate-shaped subchondral plate (Fig. 5 *E*).

As far as physical property is concerned, the fibrils and matrix permit an unusual amount of elasticity in the articular cartilage. In fact, studies have revealed that each articular cartilage possesses a relative coefficiency of elasticity which varies in different segments of its surface.[9] A certain maximum amount of force may be applied against articular cartilage which will be cushioned or absorbed without producing any permanent damage to the fibrils or matrix. A force exceeding such known amounts, resulting from an injury or strain, or a normal amount of pressure sustained over a prolonged period of time as following strenuous activity may disturb the elasticity and permanently alter the quality of the constituents of the cartilage. Following such application of abnormal forces, some parts of the matrix become disrupted, which results in desiccation and inelasticity of the articular cartilage. When this occurs, the fibrils are relatively more exposed to the articular cavity and the articular surface becomes dull, velvety, and cracked. With active and passive movements of the limbs, such changes predispose to additional damage with the formation of gross tears or fissures.

In anomalous patellae, it appears that the cartilage covering the ossicle is usually irritated because of its abnormal proximity to the femoral condyles. Radiographic examinations made in the "jackknife position" reveal that these ossicles frequently project beyond the normal articular level of the body of the patella (Fig. 1 *B*) and are, therefore, more susceptible to irritation by the opposing femoral articular cartilage.

When an injury or strain produces a tear or crack of the central area of the articular cartilage of the patella or that of an ossicle without fracturing the underlying bone, healing of the damaged cartilage may never occur. Experimental data have revealed that tears or fissures in the articular cartilage will not be completely repaired without the aid of blood supply from the subchondral marrow or from the synovial-capsular tissues.[10] On the basis of the study of our clinical material, however, we believe that small superficial tears of the outer layer of the articular cartilage may heal by "shedding the flakes." These tiny tabs of articular cartilage may be ground down to cartilage dust and finally become embedded into the synovial tissues or float about in the synovial fluid. The severer and chronic forms require surgical intervention. This is done, first, to remove the cracked or torn articular cartilage, second, to make openings into the exposed subchondral bone plate to aid in the repair of the defect of the articular surface, and, third, to remove the anomalous ossicle. Prolonged delay in such surgical procedures in the severe forms will result in progression of the tears of the articular cartilage and premature appearance of osteoarthritis of the patella.

It is also the purpose of this discussion to reiterate that tears of the articular cartilage per se may carry a much graver prognosis than simple undisplaced fractures of the patella. In such fresh fractures of the patella of the young

adult, as recently observed in two post-mortem examinations,* there was no gross irregular splintering or flaking of the articular cartilage. The openings into the subchondral bone caused by the fracture are avenues for the permeation of granulation tissue to aid in the healing of the fractured articular cartilages. Such conditions do not exist in tears of the articular cartilage per se.

SUMMARY AND CONCLUSIONS

This study of fifty-eight cases has revealed that injury to, or excessive strain on, the knee may lead to fissure and tears of the articular cartilage of the patella of the young adult. The articular cartilages covering the ossicles in the anomalous patellae may be similarly affected by trauma. The symptoms and signs caused by fissures of the articular cartilage of the patella may suggest to the examiner an injury to the semilunar cartilages, external ligaments, or synovial lining, unless one pays special attention to the patella during the examination of the knee.

While small superficial tears of the articular cartilage will probably desquamate without the aid of surgical intervention, deep cracks or fissures in the central portion of the cartilage will not heal without surgical interference. If such surgical treatment is not pursued in patients with symptoms of long standing, a progression or spread of the tears of the cartilage will probably ensue. As part of the conservative program or during the postoperative regimen, limitation of arduous activities to the affected knee for indefinite periods is indicated in order to prevent recurrence of damage to the articular cartilage. In contradistinction to other lesions in the knee, the conservative or surgical treatment of tears or cracks of the articular cartilage of the patella does not usually lead to a permanent cure due to high susceptibility of such patellae to damage following minimal injuries or exertions. Nevertheless, surgical intervention is indicated in certain instances in order to abort progression of the lesion and to aid in its healing.

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INGUINAL HERNIAS AND ALLIED DEFECTS IN NAVAL RECRUITS

An Analysis of 1,406 Patients Admitted for Surgical Treatment

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IN THESE days it is only natural that surgical thought should be principally concerned with those great strides being made in the care of traumatic injuries. The first reports, now becoming available, from the Medical Corps of the Army and Navy in the combatant areas in all quarters of the world are superior to any previously recorded, and would have been entirely impossible only a few years ago.

However, during the first two years of World War II the task was primarily one of assembling, equipping, and training those forces to be used offensively on many fronts. A tremendous volume of corrective surgery was done in personnel by medical officers on the mainland during this period of preparation to remedy physical defects existing prior to enlistment and to bring the general physical condition of our forces to the highest possible level. In one Naval installation a series of 1,406 recruits with inguinal defects were admitted for surgical treatment during a twelve-month period. An analysis of this group of patients, with a discussion of certain technical details in their care and the management of complications, forms the basis of this report.

Tabulated in Table I are the various types of inguinal defects encountered in this series of 1,406 recruits in order of their frequency. The small number of patients with epigastric, incisional, and femoral hernias admitted are included to emphasize the fact that they were infrequently observed.

Uncomplicated inguinal hernias were by far the most common lesions for which patients were admitted for repair, the next most common being inguinal hernias with cryptorchidism, inguinal hernias with varicocele, and uncomplicated hydrocele in that order.

The incidence of inguinal hernias in men of military age examined during World War II is not yet public information. Coley[1] stated that 2 per cent of those examined during World War I were found to have such defects. It seems likely that with a more complete mobilization in this war, the incidence will be as high or even higher.

Coyer and Widder[2] recently reported an incidence of 3.71 per cent actual hernias in a large group of white male defense workers between 18 and 50 years of age, the figure being 9.2 per cent in a smaller group above 50 years of age.

In civilian practice indirect inguinal hernias are said to constitute approximately 93 per cent of all inguinal hernias while direct inguinal hernias will comprise from 2 to 10 per cent of any series, depending upon the average age of

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TABLE I. INGUINAL LESIONS AND ASSOCIATED CONDITIONS EXISTING PRIOR TO ENLISTMENT

TYPE	NUMBER OF CASES	PER CENT SERIES
Inguinal hernia	1,073	76.4
Inguinal hernia with undescended testicle	97	6.8
Inguinal hernia with varicocele	66	4.6
Hydrocele, no hernia	56	3.9
Inguinal hernia with hydrocele	39	2.8
Varicocele (large), no hernia	37	2.7
Epigastric and incisional hernia	32	2.3
Femoral hernia	4	0.3
Inguinal hernia, varicocele, hydrocele	2	0.2
Total	1,406	100

the men examined. Coley[1] stated that femoral hernias, while representing 10 per cent of all hernias in both sexes, will be present in only 2.5 per cent of any series of male patients with hernia. In this period of observation only four recruits were admitted with femoral hernias for repair, an incidence of .3 per cent of the total group.

This series of men under discussion ranged in age from 17 to 35, the majority being between 17 and 24 years of age. Such a group represents a survey of young men in good physical condition, fit for vigorous military life except for the defects with which they were admitted (Table II). It is noteworthy that in the 1,073 recruits with uncomplicated inguinal hernias, indirect inguinal hernias were present in 91.8 per cent, direct inguinal hernias in 8.2 per cent, and bilateral lesions in 10 per cent. Direct hernias were seen with much greater frequency in those recruits between the ages of 25 and 35 years, being particularly common in those of short stature with a tendency to be overweight. As in the older age groups, direct hernias in these young men were usually bilateral. Unilateral inguinal hernias were consistently seen with greater frequency on the right side in an approximate rate of 6:4. This finding is in keeping with other reported experience.

TABLE II. UNCOMPLICATED INGUINAL HERNIA, SERIES OF 1,073 CASES

TYPE	NUMBER OF CASES	PER CENT SERIES
Inguinal hernia, indirect	986	91.8
Inguinal hernia, direct	87	8.2
Inguinal hernia, bilateral	108	10.0
Inguinal hernia, right	560	58.0
Inguinal hernia, left	405	42.0
Inguinal hernia, complete	307	28.6
Inguinal hernia, incomplete	766	71.4
Inguinal hernia, recurrent	20	1.8

In this series of cases the final diagnosis as to the completeness of a hernia was always made in the operating room. Hernias were considered to be complete in which a well-formed sac could be demonstrated extending down to the upper pole of the testicle or completely incorporating this structure. Since the majority of these indirect inguinal hernias were of the congenital type, one would expect a relatively high incidence of complete hernias. On the basis of the criterion listed, 28.6 per cent of this group of inguinal hernias were considered to be complete.

Twenty recruits were admitted for correction of recurrent indirect inguinal hernia, a previous surgical repair having been done prior to their entrance into the service. In every instance careful dissection at operation demonstrated a well-formed indirect inguinal sac varying in length from 4 to 12 cm. These findings confirm the established opinion that the essential step in the successful cure of indirect inguinal hernia in young patients is high ligation of the neck of the sac with complete removal of this structure.

A series of 298 cases was observed in which a hydrocele, varicocele, or an undescended testicle was present in the inguinal canal with or without an associated inguinal hernia (Table III).

TABLE III. HYDROCELE, VARICOCELE, AND UNDESCENDED TESTIS, WITH AND WITHOUT ASSOCIATED INGUINAL HERNIA, SERIES OF 298 CASES

TYPE	RIGHT	LEFT	BILATERAL	TOTAL
Hydrocele, no associated hernia	40	17	1	58
Hydrocele and inguinal hernia	22	17	1	40
Hydrocele, varicocele, inguinal hernia	0	2	1	3
Varicocele, no associated hernia	2	34	1	37
Varicocele and inguinal hernia	0	63	0	63
Undescended testicle, inguinal hernia	34	59	2	95
Undescended testicle, no inguinal hernia	1	1	0	2
Total				298

Hydroceles were noted more commonly without an associated hernia, and when this lesion was found alone, it was seen more than twice as frequently on the right side. Recruits with varicocele and inguinal hernia were admitted two times as frequently as were those with varicocele alone, since only those with large venous plexuses and definite symptoms were hospitalized for surgical correction in the absence of a hernia. The lesion was left-sided in all but two instances in these 100 cases in which a varicocele was present with or without an associated hernia.

Ninety-five recruits were admitted for repair of an undescended testicle with associated inguinal hernia. In only two cases was an inguinal testicle demonstrated in the absence of a patent hernial sac. The undescended testicle was found in an intraperitoneal position in only two instances, it having been arrested in its descent somewhere along the inguinal canal in the remaining ninety-five. In this age group the retained testicles were consistently found to be markedly atrophic, particularly those retained in the region of the internal inguinal ring.

Certain facts have been impressed upon us in making a clinical diagnosis of inguinal hernia in these patients. A complete inguinal hernia extending into the scrotum offers no problem in diagnosis, but an incomplete inguinal hernia or one with a long narrow sac may be extremely difficult to demonstrate on a single examination. We were repeatedly impressed with the accuracy of those medical officers who each day examined large numbers of incoming recruits in the reception center and referred those with inguinal hernias for surgical care. On several occasions we were unable to demonstrate conclusively a hernial sac on our first examination and after considerable debate have operated upon such an

individual admitted with a diagnosis of hernia only to demonstrate a complete well-formed sac in the canal. The logical conclusion is that these recruits when examined at the reception center had been on their feet for long periods of time, and had been subjected to various strains and exercises which greatly aided in demonstrating any hernial protrusion.

All patients in whom the diagnosis is questionable should be examined after they have remained on their feet for an hour or two during which time walking, stooping, and straining are encouraged. Both the erect and recumbent positions should be used in examination. We have found that the protruding sac can be demonstrated more frequently by straining, as in defecation, than by coughing. In the absence of a visible and palpable protrusion into the scrotum, our criterion for the diagnosis of an inguinal hernia has been the ability to palpate a definite sac within the external ring which fills, distends, and with straining can be definitely felt at the outlet of the ring. In general, the sac demonstrated at operation in questionable cases was larger and more complete than we expected to find in our early experience with this series of cases.

The surgical repair in these cases was done by four surgeons all using essentially the same technique. Spinal anesthesia was employed in the entire series, metycaine 10 per cent solution being used in 598 cases and novocain crystals or pontocaine in the 808 remaining cases. A total of ten partial anesthetic failures occurred, being much more common with novocain than metycaine.[3] However, in our hands metycaine produced an alarmingly high sensory anesthesia on several occasions which led to the routine use of novocain or its combination with pontocaine.

In the surgical care of the 1,073 patients with uncomplicated inguinal hernias a Bassini type of repair was used in 85 per cent of cases, a Ferguson in 7 per cent, the cord transplanted to the subcutaneous tissues in 7 per cent, and the McVay technique in 1 per cent. Before removal of the hernial sac, high ligation of its neck was routinely practiced but transfixion to the adjacent structures at the internal ring was not considered an essential step. Every effort was made to avoid tension in completing the hernial repair. The anterior edge of the lower rectus muscle sheath was frequently divided in a longitudinal direction 1.5 cm. medial to its lateral edge to permit more simple closure, when the conjoined tendon could not be readily sutured to the shelving edge of Poupart's ligament without tension. Both hydroceles and varicoceles were routinely exposed by an inguinal incision rather than through the upper scrotum because of the frequent association of hernias and the better wounds which resulted. Hydroceles were corrected by a modified "bottle operation" after as complete removal of the sac as was possible. Various types of operative procedures were employed for the correction of the large varicoceles. The most satisfactory results followed a removal of the anterior two-thirds of the venous plexus from the internal ring to the upper pole of the testicle, preserving the vas deferens and the spermatic artery.

In those patients presenting with an undescended testicle and inguinal hernia, the hernial sac was completely removed and every effort made to replace the testicle in the scrotum by lengthening the cord. A Ferguson herniorrhaphy was performed when scrotal replacement of the testicle was possible. Multiple staged procedures to replace a retained testicle in the scrotum were not practiced. When the inguinal testicle was small and atrophic and could not be replaced in the scrotum, orchidectomy was the procedure of choice when a normal testicle was present on the opposite side. Experience amply demonstrated that a testicle retained in the lower inguinal canal or over the symphysis pubes produced marked discomfort when recruits were subjected to a vigorous physical training program.

This group of young men in excellent physical condition, of similar age, and with comparable defects offered an ideal series in which to study wound healing with various suture materials. Chromic catgut, fine steel wire, and cotton thread were selected as the materials to be used under careful control.

Because of the known frequency with which hernial wounds become contaminated, a strict routine for preoperative preparation of the operative field was established during the first month of this study. The generous use of soap and water during the preoperative evening was the essential feature in the preparation of the inguinal areas; following this the field was covered with a sterile towel securely taped in place and not disturbed until the spinal anesthetic had been given. The inguinal regions were then cleansed with ether and painted with a standard antiseptic solution.

Chromic catgut in sizes No. 0 and 1 was used for repair of the hernia with No. 000 chromic or plain No. 0 for fine ties in one series of cases. A second series of cases was observed using fine steel wire and chromic No. 000 for ties. When cotton thread was employed No. 50 white was used for superficial ties and the hernial repair carried out with either No. 24 or 30 white thread. In a series of 239 consecutive cases, 1 Gm. of sulfanilamide powder was placed in the superficial fat before closure and its effect on wound healing noted.

For the first quarter of this study (300 cases) the dressings were changed on the third postoperative day and again on the seventh day after operation when the sutures were removed. In the remaining period (1,100 cases) the dressings were not disturbed until the seventh postoperative day unless specifically indicated, and pressure dressings utilizing two gauze rolls were routinely employed. All wounds were carefully graded and classified as having healed by primary union or as complicated grade A, B, or C. An "A" wound referred to a serum collection or small hematoma which in no way materially delayed convalescence or interfered with the wound integrity. Wounds classified as "B" evidenced a small stitch abscess which promptly responded to therapy in forty-eight to seventy-two hours. Type "C" wounds were those in which a frank infection developed, necessitating opening of the incision and producing a definite delay in convalescence and potential interference with the integrity of the wound.

The results of this study in wound healing are tabulated in Table IV. The wounds obtained using white cotton thread in sizes No. 50 for ties and No. 24

TABLE IV. WOUND COMPLICATIONS, SERIES OF 1,406 PATIENTS WITH INGUINAL DEFECTS REPAIRED WITH DIFFERENT SUTURE MATERIALS

MATERIAL	NUMBER OF CASES	"A" COMPLICATION		"B" COMPLICATION		"C" COMPLICATION	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Chromic No. 1, plain No. 0	165	31	18.7	1	0.6	9	5.4
Chromic No. 0, chromic No. 000(S)	114	8	7.0	1	0.8	3	2.6
Steel wire, chromic No. 000(S)	30	5	16.0	0	0.0	0	0.0
Cotton No. 24, No. 50(S*)	95	7	7.3	1	1.0	0	0.0
Cotton No. 24, No. 50	301	17	5.6	0	0.0	0	0.0
Cotton No. 24, No. 50 (P†)	701	14	2.0	3	0.42	7	0.27

Twenty-six of 82 type "A" wounds (32 per cent) due to hematomas.
*S indicates 1 Gm. of sulfanilamide in wound.
†P refers to pressure wound dressing.

for the hernial repair together with a pressure dressing were so strikingly superior that this type of suture was routinely adopted for use in all general surgical procedures. Fine cotton suture material has the obvious advantages of low cost, ready availability, simple sterilization, and ease of handling. With its use the incidence of type "A" wound complications (serum or hematomas) was reduced to 2 per cent in the last 701 patients submitted to corrective inguinal procedures. The induration which usually characterizes a hernial wound closed with catgut, especially in the larger sizes, has been striking by its absence in this series of cotton wounds. In no instance has a draining sinus developed necessitating exploration of the wound to remove retained cotton knots. It is interesting to note that the introduction of 1 Gm. of sulfanilamide powder into the superficial fat of these wounds before closure, using both fine catgut and cotton suture material, consistently tripled the incidence of serum collections subsequently requiring evacuation.

The incidence of Type "B" and "C" wound complications referring to stitch abscesses or frank wound infections, respectively, was 1.4 per cent for this series of inguinal procedures. In the five wounds in which infection developed after closure with cotton, the subsequent healing time was quite comparable to that seen with a similar wound infection when catgut had been used as the suture material. We feel that cotton suture material is a very worth-while addition to our surgical armamentarium and will become increasingly popular with surgeons in the postwar era.

Postoperative pulmonary complications occurred in 2.4 per cent of this series of 1,407 consecutive inguinal procedures. Atelectasis, both lobar and lobular, and bronchiopneumonia were the most frequent chest complications encountered in the order named. In every instance there was a prompt and satisfactory recovery with appropriate therapeutic measures.

Postoperative urinary retention early presented itself as a complication of the first magnitude in this group of young men, in none of whom was organic urinary tract pathology present (Table V). In the first 301 operations, eighteen hours were allowed to pass following surgery before catheterization was resorted to if the patient was unable to void. Using ordinary conservative measures, the incidence of urinary retention in this group was 19.9 per cent. The use of the

TABLE V. POSTOPERATIVE URINARY RETENTION IN A SERIES OF 1,371 PATIENTS FOLLOWING INGUINAL PROCEDURES

NUMBER OF CASES	THERAPY	PATIENTS REQUIRING CATHETERIZATION	PER CENT REQUIRING CATHETERIZATION
301	C. M.,* 18 hours	60	19.9
202	C. M., prostigmine 1:4000	48	23.7
242	C. M., prostigmine 1:2000 (up patients)	10	4.1
240	C. M., sterile saline (up patients)	1	0.41
152	C. M., prostigmine 1:2000	3	1.9
65	C. M., sterile saline	3	4.6
169	C. M., 24 hours	2	1.2
1,371		127	9.2 Average

*C. M., Conservative measures.

same conservative measures plus prostigmine 1:4000 for a total of eight doses had no effect in reducing the incidence of retention in a second group of 202 cases. Prostigmine 1:2000 solution was then adopted, one injection being given at 6 A.M. on the morning of surgery and seven injections following operation at four-hour intervals. In addition to this, twenty-four hours were allowed to pass following operation unless the patients were definitely uncomfortable and they were permitted to stand at the bedside to void if necessary. This latter procedure was considered entirely safe after the general adoption of cotton suture material for wound closure. With this routine the incidence of postoperative urinary retention fell abruptly to 4.1 per cent. This improvement was so dramatic that normal saline solution was substituted for the prostigmine solution without knowledge of the ward personnel, all other measures being continued. The results were even more striking, the incidence of retention dropping to .41 per cent.

Further series of cases were observed with the use of both prostigmine 1:2000 solution and normal saline solution, but again the patients were prohibited from standing at the bedside to void. In these two series the incidence of retention requiring catheterization was 1.9 and 4.6. A final group of 169 patients was observed in which no medication was employed, no patient was permitted out of bed, and twenty-four hours were allowed to pass in all cases before catheterization. The incidence of retention in this group was 1.2 per cent.

We concluded from this study that prostigmine was not primarily responsible for the reduction in the incidence of urinary retention in these young individuals.[4] The important factors were allowing twenty-four hours to pass before insisting that the bladder be emptied, permitting the sitting or standing position to void if surgically feasible, and providing good nursing care.

Unfortunately, it is impossible to have available the figures on recurrence in this series of inguinal defects subjected to surgical repair. To our knowledge, none of these patients have reported to date with a recurrence, although it is a well-established fact that these may be expected within the first year following surgical repair. Watson[5] stated that the recurrence rate for indirect inguinal hernias varied from 1 to 10 per cent, being lowest in the age group from 10 to 45 years, while the incidence of recurrence with direct inguinal hernias was from 10 to 20 per cent in the most experienced hands.

Recurrences undoubtedly will develop in some instances while these men remain on active duty and will be discovered in the course of the periodic physical examinations to which all Naval personnel are subjected. However, the incidence should be low since these men represent a group of healthy young individuals with excellent tissue and the hernias in the majority of instances were of the congenital type.

There was no mortality in the group of 1,407 recruits subjected to surgical repair of their inguinal defects, all having returned to a duty status. Through this program all these men were restored to a state of more complete physical fitness and were able to take their full part with the armed forces.

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Editorial

The Use of Chemotherapy in the Secondary Closure of War Wounds of Soft Parts

AN ANALYSIS of the experience of various surgeons with the secondary suture of war wounds of the soft parts reveals important discrepancies in technique. Failure to recognize these discrepancies has resulted in confusion concerning the use of chemotherapy as an adjuvant to the secondary suture of wounds of the soft parts.

The reported experience may be segregated into three main categories:

1. Secondary suture or skin grafting *at the time of removal of the first dressing* subsequent to initial surgery. Sulfonamide is given after initial surgery but is discontinued at the time of surgical closure of the wound. Healing without infection occurs in 90 to 95 per cent of cases.

2. Secondary suture or skin grafting of wounds dressed more than once after initial surgery. If no chemotherapy is given, healing without infection occurs in only 50 to 70 per cent of cases.

3. Secondary suture or skin grafting of wounds dressed more than once but patient given chemotherapy, usually sulfonamide, after secondary closure. Healing without infection occurs in 85 to 95 per cent of cases.

The surgeon who elects secondary closure at the time of removal of the first dressing accomplishes his objective with the least waste of time and effort and the results are as satisfactory as with any other method. Reliance is placed upon the clean surgical appearance of the wound as an index of the absence of infection.

The surgeon who elects secondary closure after two or more dressings of the wound has found it necessary to use chemotherapy, usually sulfonamide, to prevent infection. The ultimate results are comparable, but not superior, to the results attained by secondary closure at the time of the first dressing without subsequent chemotherapy.

Important clinical conclusions are permissible. The gross pathology of the wound is a reliable index of infection only when three to ten days have elapsed since the last dressing. Further, it is impractical to use bacteriologic cultures to determine the optimal time for wound closure. Contamination at the time of culture may not be revealed by the outgrowth of the coincidentally implanted organisms. The efficacy of sulfonamides in the prevention of infection in secondarily sutured wounds of the soft parts suggests that the most likely responsible pathogen is the beta hemolytic streptococcus. The bacteriologic studies of World Wars I and II support this conclusion. The efficacy of *systemically administered* sulfonamides in the therapy of impending streptococcal infection is clearly established.

It has been found by some observers that *local* sulfonamide therapy may be substituted for systemic therapy without statistically significant alteration in the incidence of infection. This attests the antistreptococcal potency of sulfonamide and the negligible risk of infection in cleanly excised wounds of the soft parts by organisms other than the hemolytic streptococcus. It does not justify the local use of irritant chemicals in any wound. Objection to the local use of sulfonamide is based in part upon a demonstrated impairment in wound healing. The currently available statistics record this impairment only in terms of wound dehiscence or the suppurative decomposition of wound exudate evoked by the antibacterial agent. It remains unproved that local sulfonamide is an essential or desirable adjuvant to the surgical management of a wound of the soft parts.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

SYMPATHECTOMY AND THE CIRCULATION—ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS AND EARLY AND LATE LIMITATIONS

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REGIONAL sympathectomy has become popular as a supplement to the conservative treatments conventionally employed for vasospastic, arterial obstructive, post-traumatic, or painful vascular diseases of arms and legs. It has also become popular in the form of splanchnicectomy for many patients with hypertension. Splanchnicectomy has been extended by Smithwick[1] and others to include a sympathetic denervation of the legs and lower trunk that approaches 50 per cent of the surface area of the body. Sympathectomy of all of the viscera and of 55 to 96 per cent of the surface area of the body has also been accomplished in patients with hypertension by subtotal to total paravertebral sympathectomy, splanchnicectomy, and celiac ganglionectomy.[2] The utility of these various forms of sympathectomy depends upon the effect on the disease process and also upon the extent and duration of anatomic and physiologic changes effected by the operation.

Encouragement is often afforded by clinical observation of favorable effects upon the disease process. The extent and duration of the effects of sympathectomy are, however, limited by anatomic and physiologic considerations that have been the subject of numerous investigations. Careful evaluation of these limitations has facilitated advances in the utility of clinical surgery. Lee,[3] Kuntz,[4] White and Smithwick,[5] Heymans and Brouha,[6] McDowall,[7] Cannon,[8] Ochsner and DeBakey,[9] Fatherree, Adson, and Allen,[10] Sheehan,[11] Langworthy,[12] Van Dellen, Scupham, de Takats, and Fowler,[13] and others have earlier reviewed various aspects of the problems related to the sympathetic nervous system and the control of the blood vessels and the circulation.

Increasing clinical experience has partially defined certain limitations of sympathectomy. Early observations indicated that loss of sweating of the hands, feet, or head was often prolonged or even permanent. There has been observed, however, some degree of recovery from the constriction of the pupil and the lid ptosis of Horner's syndrome. Observations related directly to vasomotor functions have usually depended upon indirect methods of examination that are not easily evaluated. They have indicated that the maximum increase of warmth, blood vessel pulsation, and blood flow is present during the first several days after a sympathectomy. Following this there is often a

partial early and a gradual late and usually incomplete return toward the preoperative state that limits the therapeutic effectiveness of the procedure. Clinical and experimental observations that might explain recovery phenomena will be considered first in three groups. General limitations of surgery of the sympathetic nervous system will then be discussed.

SYMPATHETIC NERVE REGENERATION

Regeneration has been considered important as a limitation of sympathectomy since the studies of early investigators. Pye-Smith[14] in 1887 reported recovery of control of the nictitating membrane, pupil, and temperature of the ear in a cat 110 days after removal of a portion of the left cervical sympathetic chain. Langley,[15, 16] Tsukaguchi,[17] Lee,[3] and others have established the ability of preganglionic fibers central to the superior cervical sympathetic ganglion in cats, dogs, and rabbits to regenerate. Functional preganglionic regeneration could be demonstrated by central stimulation in these experiments within three to eight weeks. Lee[3] brought out the remarkable ability of sympathetic nerves to bridge long defects. Regeneration occurred in one case 275 days after a one-inch separation of the cut ends of the cervical chain even though the sternomastoid muscle had been placed between the divided ends. Lee also reviewed the early literature of nerve regeneration and observed that vasomotor paralysis disappeared before sebomotor and pilomotor function returned. Tower and Richter[18] have demonstrated regeneration of divided preganglionic fibers central to the stellate ganglion in cats with return of skin resistance and skin action currents of the pads of the paws to normal. Hinsey, Phillips, and Hare[19] demonstrated preganglionic regeneration to the head and limbs of cats after various forms of sympathectomy.

Hollinshead and Finkelstein[20] demonstrated by histologic methods regeneration of the sympathetic nerve supply to the adrenal glands of cats as early as four months after sympathectomy. Haimovici and Hodes[21] demonstrated cardiac acceleration in completely sympathectomized cats and believed that this effect resulted from nerve regeneration to the adrenal glands. The phenomena of regeneration and partial recovery of sympathetic function after preganglionic sympathectomy of extremities in patients has been observed frequently by many surgeons and has been emphasized by Smithwick.[22] Kirgis and Ohler[23] described histologic evidence of regeneration after sympathetic ganglionectomy in cats. They observed functional regeneration to the eye but not to the leg or foot.

The ability of postganglionic sympathetic nerve fibers to regenerate has also been investigated. Tuckett[24] in 1896 obtained evidence of regeneration of postganglionic fibers from the superior cervical ganglion of a rabbit in 259 days. Machida[25] found regeneration as early as fifty-seven days and also noticed that vasomotor recovery preceded recovery of the pupil. Tower and Richter[26] found no evidence in the paws of cats of recovery of sweating or decrease of skin resistance that might indicate functional regeneration one to one and one-half years after division of the sympathetic fibers from the stel-

late ganglion. Hinsey, Phillips, and Hare[19] found no evidence of regeneration to the forepads of cats 236 days after removing the thoracic chain from the stellate through the eighth thoracic ganglion. Kilvington and Osborne[27] reported return of vasomotor reflexes as determined by the plethysmograph 205 days after section of the sciatic nerve of dogs. Trotter and Davies[28] observed recovery of sebomotor and pilomotor function six to eight months after peripheral nerve section performed upon themselves. Kredel and Phemister[29] have demonstrated varying degrees of restoration of vasomotor, pilomotor, and sebomotor function in pedicle skin flaps in which nerve and blood supply had been completely severed in stages. Recovery of central vasomotor tone and of a vasoconstrictor mechanism capable of response to central stimulation has been reported in completely sympathectomized dogs.[30] Histologic evidence of sympathetic nerve regeneration that might explain the incomplete vasomotor recovery observed was described. Additional unpublished studies by F. E. Kredel, H. Wilson, and D. B. Clark of blocks of tissue removed from the scar of excision of the sympathetic chain of these dogs have demonstrated that regenerating fibers leave the divided sympathetic rami and enter and follow along the scar. Sympathetic fibers were few and scattered in the first few weeks. However, one year or more after sympathectomy, definite nerve bundles coursed along through the scar. Simmons and Sheehan[31] demonstrated by ulnar nerve block evidence of regeneration in patients having a late relapse after ganglionectomy or preganglionic sympathectomy performed for acrocyanosis, Raynaud's disease, or scleroderma of the upper arm.

These reports and many others demonstrate that nerve regeneration and a varying amount of recovery of function may occur after division or excision of sympathetic nerves and ganglia. While this process may limit the enduring effectiveness of regional or total sympathectomy it probably does not explain the early partial recovery of vascular tone. Two factors that play a role in the early recovery will next be considered.

INCREASED IRRITABILITY OF SMOOTH MUSCLE AFTER SYMPATHECTOMY

An increased responsiveness of denervated smooth muscle to blood-borne vasoconstrictor or vasodilator substances might limit the early effectiveness of sympathectomy. Bernard[32] in 1852 divided the cervical sympathetic chain below the superior cervical ganglion in animals and observed turgescence of blood vessels and increased warmth in the denervated area. He recognized that the enlargement of the blood vessels diminished within several hours and might not be visible one day after nerve section but that the warmth persisted several months and was maintained during exposure to cold. He later observed[33] that the paralytic effect of removal of the superior cervical ganglion was more rapid, more intense, and greater than that produced by simple section of the cervical sympathetic chain and that it might last at least one and one-half years in the dog.

Degeneration of postganglionic sympathetic nerve fibers was employed by Lewandowsky[34] and Langley,[35] who excised the superior cervical ganglion, and by Brodie and Dixon,[36] who divided the sciatic and anterior crural nerves, to

demonstrate that adrenalin had a peripheral action. Meltzer and Meltzer[37] studied the circulation of the rabbit's ear after unilateral resection of the sympathetic chain or the superior cervical ganglion. They observed that the constriction of the blood vessels produced by intravenous adrenalin began later, developed more slowly, and lasted longer in the denervated than in the opposite ear. They also observed[38] that dilatation of the vessels of the normal ear and constriction of those in the sympathectomized ear followed moderate amounts of adrenalin introduced subcutaneously. They concluded that varying degrees of sympathetic vasoconstriction and vasodilatation of central origin modify the peripheral action of adrenalin in the normal ear and that the phenomena observed in the sympathectomized ear represents the peripheral action of adrenalin freed from these central influences.

An essential difference between division of the cervical sympathetic chain, preganglionic sympathectomy, and excision of the superior cervical ganglion, ganglionectomy, was described by Meltzer and Auer[39] in rabbits and Meltzer[40] in cats. They observed that subcutaneous adrenalin had no effect on the normal pupil or upon the pupil denervated by preganglionic sympathectomy but that it produced maximum dilatation of the pupil denervated by ganglionectomy. This effect was first evident twenty-four to forty-eight hours after ganglionectomy and continued during a three and one-half month period of observation. Elliott[41] extended these studies to include the smooth muscle of blood vessels and noted that the increased irritability persisted at least ten months. He also noticed that some degree of increased irritability followed preganglionic sympathectomy. He stated, "This, then, is true for all the muscles thrown into contraction by adrenalin, that after decentralization (i.e., degenerative section of the preganglionic sympathetic nerves), and still more clearly after denervation (degenerative section of the post-ganglionic sympathetic nerves), they contract in the presence of adrenalin alike with greater irritability and persistence."

Dale and Richards[42] demonstrated that the blood vessels of cats were rendered abnormally sensitive to the vasodilator action of histamine and acetylcholine as well as to the constrictor action of adrenalin by complete degeneration of their nerve supply.

Rosenbleuth and Cannon[43] studied the effect of sympathin on the nictitating membrane of the cat after removal of the superior cervical ganglion and determined that contraction would occur only after "sensitization" of the animal by cocaine injection. Hempel[44] also studied adrenin and the nictitating membrane of the cat and observed that the increased response following section of the cervical sympathetic chain is about one-half as great as that which follows denervation by ganglionectomy. He reviewed the theories advanced to explain the increased "sensitivity" and favors the Rosenbleuth proposal that an increase in permeability of the denervated cells after sympathectomy is responsible.

Freeman, Smithwick, and White[45] employed intravenous adrenalin and insulin hypoglycemia in patients and observed an abnormal lowering of skin

temperature that developed six or eight days after removal or alcohol injection of the sympathetic ganglia. This effect was also observed during insulin hypoglycemia in rabbits and cats. Removal of one adrenal and denervation of the other prevented the vascular constriction which usually accompanied hypoglycemia in animals. Smithwick, Freeman, and White[46] considered the possible relationship of this "hypersensitivity" to the recurrence of vascular spasm in Raynaud's or vasospastic disease that often occurred after upper arm sympathetic ganglionectomy. Four patients treated by cervicodorsal ganglionectomy demonstrated a marked degree of vasospasm following intravenous epinephrine. Three of these, ten days, twenty-two days, and ten months, respectively, after operation, had a marked clinical recurrence of spasm, and one three months after operation had no clinical recurrence. Two patients after lumbar ganglionectomy had marked and moderate spasm with epinephrine, although clinical recurrence was slight or absent at twenty-two days and at ten months. One other patient described had an incomplete sympathectomy and three had no note concerning clinical recurrence. These authors concluded from these limited clinical studies that hypersensitivity to circulating epinephrine may constitute an important source of unsatisfactory results of sympathetic ganglionectomy for Raynaud's disease.

Grant[47] studied the vasomotor reaction of the rabbit's ear to changes of room and body temperature, nervous and muscular activity, and adrenalin. Increased responsiveness of denervated vessels developed during five to seven days and then remained constant during nine-, thirteen-, and fifteen-month periods of observation. One rabbit, however, regained constriction of the ear vessels between thirteen and eighteen months after excision of the superior cervical and stellate ganglia. Preganglionic sympathectomy was also observed to produce an enhanced responsiveness although less than that produced by removal of the ganglia. The reactions of the normal and the denervated ears were not altered by adrenalectomy or by removal of the pituitary body. Grant believed, therefore, that under conditions of nervous and muscular activity an adrenalin-like substance, probably not sympathin, circulates through the blood from some unknown source. This substance was thought to play a role in maintaining normal vascular tone and body temperature and in stimulating the increased responses observed in denervated vessels.

White, Okelberry, and Whitelaw[48] made further observations on the denervated rabbit's ear and on the hands of two monkeys. Following denervation of one hand of the monkeys by ganglionectomy 1 c.c. of 1 to 1,000 epinephrine produced a surface temperature lowering from 86 to 74.5° F. in one animal and 0.25 c.c. produced a fall from 88.5 to 81.5° F. in the other. The temperature of the control hands was not changed. In addition the spinal roots from the fourth thoracic vertebra through the tenth were divided on the side of the control hand of one monkey. Epinephrine (0.25 c.c.) later produced a lowering of the temperature of this hand from 89 to 85° F. and a lowering of the hand denervated by ganglionectomy from 87.5 to 79.5° F. These authors believed that this "sensitization" phenomenon accounts for re-

currence of vasospasm. They also believed that since leg denervations are usually preganglionic this may explain the better effects of sympathectomy of the leg than the arm of patients with Raynaud's disease.

Ascroft,[49] working in the laboratory of physiology at Yale in 1935 and 1936, studied the reaction to local cold and to adrenalin in twelve monkeys that had undergone cervicothoracic ganglionectomy and eight that had preganglionic sympathectomy. Nine of the twelve reacted to local cold as well as did the normal limb; two reacted more intensely than did the normal; and in only one did a good degree of vasodilatation persist. Each of the eight that had preganglionic sympathectomy developed less reaction to cold than did the normal limbs. Adrenalin "sensitization" occurred in all of the sympathectomized limbs. After preganglionic sympathectomy the reaction to adrenalin was three times as great as in the normal limb and after ganglionectomy it was ten times normal. Ascroft also noted an opposite order of "sensitization" for pitressin and ephedrine. Preganglionic sympathectomies produced more "sensitization" to these drugs than ganglionectomies. Denervation of one adrenal gland and removal of the other in two monkeys did not prevent abnormal response to cold of hands denervated by ganglionectomy. This observation agrees with that of Grant[47] and indicates that the adrenal medulla is not solely responsible for all of the observed "sensitization" phenomena.

Freeman, White, Smithwick, and others quoted have stated that preganglionic sympathectomy might be more beneficial than ganglionectomy in the treatment of patients with vasospastic peripheral vascular diease. Telford[50] and Smithwick[51] in 1935 independently performed preganglionic sympathectomies rather than ganglionectomies for vasospastic diseases of the arms of patients. Reports of these authors were encouraging. Lewis[52] presented six patients treated by preganglionic sympathectomy for Raynaud's disease of the hands that early demonstrated clinical improvement. In five of the six, vasospastic attacks recurred spontaneously or could be produced by cold and occlusion. He concluded that these attacks are related to some local fault of the blood vessels since central vasoconstrictor nervous influences had been elimnated by the sympathectomy and since sensitization by ganglionectomy or preganglionic sympathectomy of the blood vessels of arms of patients that have no pre-existing vasospastic disease does not produce Raynaud's disease or similar clinically significant sensitization phenomena. Simmons and Sheehan[31] emphasized the significance of this local fault in the early relapse following sympathectomy and the importance of nerve regeneration in the late relapse. Among thirty-three complete ganglionectomies, early relapse occurred in nine, late relapse in twenty, and no relapse in four. Among twenty-eight preganglionic sympathectomies, early relapse occurred in four, late relapse in seventeen, and no relapse in seven. Longer observation of this second later series might have further altered the group proportions. Ulnar nerve block by novocain gave increased temperature of the little finger in the patients with late relapse that in view of control studies would seem to indicate regeneration.

Late relapse usually occurred six to nine months after ganglionectomy and as early as three months after preganglionic sympathectomy. White[53] summarized the surgical opinion developed during the first three or four years of clinical use of preganglionic sympathectomy. He stated that most surgeons agree that ganglionectomy no longer should be done because of the associated increased sensitivity of the smooth muscle of the arterioles.

Fatherree and Allen[54] and later Fatherree, Adson, and Allen[10] after many carefully controlled clinical experiments disagreed with the clinical observations and conclusions of Smithwick, Freeman, and White quoted previously. The first report[54] controlled the experimental conditions necessary for an accurate evaluation, by skin temperature observations, of the effect of injecting epinephrine. They demonstrated that the vasoconstrictor effect of epinephrine varies widely in normal individuals and is not necessarily exaggerated in patients with Raynaud's disease. Their second report[10] demonstrated that sympathectomy of the upper extremity of man by removal of the ganglia (postganglionic sympathectomy) does not produce nearly as great a "sensitivity" of smooth muscle as it does in monkeys. Preganglionic sympathectomy and postganglionic section (ganglionectomy) of the hand of patients each effected a decrease in cutaneous temperature in response to standard doses of epinephrine that was approximately twice that observed before operation. These authors concluded: "The problem of unsatisfactory results that occasionally follow operation for Raynaud's disease of the hands has not been satisfactorily solved by a study of sensitivity of digital arterioles to epinephrine." This conclusion is in agreement with the opinion of many surgeons and myself that these unsatisfactory results have not been materially solved by operations employing the preganglionic sympathectomy technique.

These reports of increased irritability of smooth muscle after sympathectomy indicate that sensitization phenomena develop shortly after any form of sympathectomy, reach their maximum within two weeks, and then persist unless regeneration occurs. These phenomena may limit the early effectiveness of any sympathectomy during periods of local cold or during circulation of adrenalin and adrenalin-like substances in the blood stream. It would seem evident now that ganglionectomy, as described for the upper arm by Adson and Brown[55] and by Gask,[56] is associated with less risk of regeneration, but more of "sensitization," while preganglionic sympathectomy, as carried out by Telford[50] and Smithwick[51] involves greater risk of regeneration and less of "sensitization." Further considerations related to the decision between these two types of operations will be described.

RECOVERY OF INTRINSIC PERIPHERAL VASCULAR TONE AFTER SYMPATHECTOMY

The inherent ability of the smooth muscle of blood vessels to maintain an independent tone probably limits the early and late effectiveness of sympathectomy more than any other single factor. The finer arteries and arterioles containing smooth muscle, and the much greater capillary bed, are largely

responsible for maintenance of the peripheral resistance to the flow of blood. The sympathetic nerve supply to these arteries and arterioles, and to some extent to the capillaries, largely modulates and only partially maintains vascular tone. This is true also of humoral influences. The ability of smooth muscle to develop and maintain a significant degree of tone even though deprived of nerve and humoral control has been demonstrated by many experiments and is generally accepted. References will here be limited to early perfusion experiments, the effect of carotid sinus and depressor nerve stimulation, and the effect of cord destruction and total sympathectomy.

Perfusion of isolated organs or limbs by Ringer's solution, by solutions of gum arabic, and by other blood substitutes that did not contain adrenalin or other blood-borne humoral elements, was employed in many early physiologic and pharmacologic experiments. Since denervation by amputation was usually performed immediately before perfusion, a maximum smooth muscle relaxation and increase of flow was present. A gradual increase of resistance and decrease of flow were often observed during the course of an experiment even though the capillary bed deprived of oxygen relaxed. Dale[57] demonstrated that acetylcholine would reverse this tendency and produce increased flow through the perfused ear of a rabbit. Dale and Richards[42] demonstrated that acetylcholine produced dilatation of vessels of perfused organs or of separated arteries under the simplest conditions. They also demonstrated that the legs of cats denervated sixteen days before amputation and perfusion were abnormally sensitive to the vasodilation action of histamine, adrenalin, and acetylcholine. These and many other perfusion experiments have indicated that the blood vessels after denervation recover, maintain a degree of tone, and are capable of dilatation. They are not completely or permanently dilated by denervation and elimination of humoral influences. A gradual increase of the degree of tone is evident during the first hours or days after denervation, and the increased tone is maintained.

Heymans[58] has reviewed the current concepts of reflex neurovascular regulation of blood pressure and circulation as derived from detailed experiments in his laboratory and elsewhere. The depressor nerves from the carotid sinuses and from the heart and aorta conduct impulses from pressosensitive nerve endings in these locations to the vasomotor centers that modulate or govern blood pressure. This reflex neurovascular regulation of blood pressure functions well after elimination of the secretion of the adrenal medulla, according to Nowak[59, 60] and Heymans and Bouckaert.[61] Stimulation of the modulator nerves by pressure sacs in the carotid sinus (Heymans, Donatelli, and Shen[62]) or prolonged electrical excitation (Phemister and co-workers[63]) inhibits vasoconstriction, produces active reflex vasodilatation, but only occasionally reduces blood pressure to shock levels. The latent period preceding the lowering of blood pressure is brief, indicating a reflex response and not an alteration of humoral secretion. Even under these conditions of vasoconstrictor inhibition and reflex vasodilatation, sufficient vascular tone exists to maintain circulation and, in Phemister's experiments, to resist true shock entirely in some animals and

for many hours in others. These and other experiments dealing with the proprioceptive reflex mechanisms that regulate blood pressure thus indicate that central or peripheral reflex activity modulates peripheral vascular tone but does not entirely maintain it and cannot entirely overcome it even by active vasodilatation.

Studies of circulation and blood pressure in animals after destruction of the thoracic and lumbar spinal cord, or after total paravertebral sympathectomy, also demonstrate that the peripheral vascular bed maintains and improves tone after denervation. The cord destruction experiments also yield observations relative to the circulation after a preganglionic sympathectomy of the entire body. The complete paravertebral sympathectomy experiments offer comparable studies on the effects of sympathetic ganglionectomy.

Hermann, Morin, and Vial[64, 65] have reviewed the effects of cord destruction. They demonstrated by acute experiments that ascending destruction of the spinal cord to progressively higher levels effects appreciable lowering of blood pressure only after the seventh thoracic spinal segment is reached. Further destruction of the remaining upper thoracic segments lowered the pressure to values around 50 mm. Hg. Destruction of the entire thoracic and lumbar cord was associated with a relatively normal blood pressure even though chronic experiments were continued up to one year and fifty-three days. Normal values returned within one day, or two, of the operation and were maintained. These animals with preganglionic sympathectomies of the entire vascular bed, produced by cord destruction, were extraordinarily sensitive to small doses of hypertensive pharmacologic products, such as adrenalin. These authors discussed the possibility that either a sensitization to adrenalin liberated by humoral stimulation of the denervated glands or a peripheral nervous tone arising in the decentralized sympathetic ganglionated chains might partially account for the maintained peripheral resistance.

Removal of the paravertebral sympathetic chains was first performed upon cats by Cannon and associates.[66] The effects of this procedure upon circulation have been reviewed and further investigated employing dogs.[30] The operations were carried out in three stages at intervals of several weeks. A decline of blood pressure averaging 38 mm. Hg occurred. Restoration began within a few weeks of the last stage of the sympathectomy and reached the preoperative level in an average time of six months. Blood volume and blood viscosity were not appreciably altered. Cardiac output was reduced during the stage of hypotension and also late after restoration of the blood pressure to normal values. Varying amounts of adrenalin given before and several weeks to one or two years after the sympathetic ganglionectomy produced essentially similar blood pressure responses. Blood pressure lowering seems more prolonged and adrenalin hyperresponsiveness less evident in these experiments than in those involving cord destruction.

These studies on vascular tone during perfusion of isolated organs, stimulation of carotid sinus and depressor nerves, destruction of the spinal cord, and excision of the paravertebral sympathetic chains and ganglia seem to

indicate that denervated blood vessels are capable of developing an intrinsic tone. This tone is not dependent upon nerve regeneration during the first several weeks and may occur at times under conditions that would exclude an adrenalin "sensitization" factor. Cannon[9] stated: "Until definite proof that an external agent operates to restore 'tone' in denervated vascular muscle I believe we are warranted in assuming that the restoration results from an intrinsic property of the muscle itself." This property of denervated smooth muscle probably presents the major limitation to the effectiveness of clinical sympathetic nerve surgery for vascular disease.

GENERAL LIMITATIONS OF SYMPATHECTOMY

The Role of Sympathetic Vasodilator Pathways.—There are influences in addition to the three just discussed that limit or qualify the effect of regional and extensive sympathetic denervation of the peripheral vascular bed. Operations evidently do not uniformly alter circulation through the body. A difference exists between the effect upon circulation of regional and of extensive sympathectomies. Herrick, Essex, and Baldes[67] and Schneider[68] believed from evidence obtained after lumbar sympathetic ganglionectomy of the hind leg of the dog that increased circulation may remain double the control values as long as twenty-four to thirty-four months. Sympathectomies of normal legs of patients incidentally effected by operation for megacolon produce an elevation of skin temperature that may persist many years. Essex, Herrick, Baldes, and Mann[69] determined that nine and ten years after lumbar ganglionectomy of one hind leg in a dog the blood flow returned to almost the same as that of the normal limb. Sympathectomies of the entire body of the dog[30] effect a less conspicuous change in circulation. Blood volume and viscosity are not appreciably altered and cardiac rate and output are decreased. Sympathectomies of most of the body of patients with hypertension[2, 70] have not altered venous pressure or arm-to-tongue circulation time and have slightly decreased the basal heart rate and cardiac output. Extensive or total sympathectomy does not double the rate of circulation of blood through the body as regional sympathectomy may for the leg.

This difference between the effect of regional and of total sympathectomy may be related in part to the role played by the vasodilator mechanism of the body. The effect of a sympathectomy upon each organ or body structure will vary with the relative importance of vasoconstrictor influence or tone in the regulation of its circulation. Sympathetic nerves may carry vasodilator fibers and the effect of sympathectomy will vary with the number and importance of the vasodilator fibers divided.

A complex vasodilator system exists in some animals and also in man. McDowall[7] and Burn[71] have recently summarized the current opinions related to this system. Nervous vasodilator mechanisms are in part extrasympathetic. They are related locally to Lovén reflexes, axon reflexes, and antidromic impulses. They are related centrally to vasodilator impulses that travel from centers in the medulla and spinal cord through specialized nerves such as the

chorda tympani and nervus erigens and according to some evidence through the posterior nerve roots along many sensory nerves.

Nervous vasodilator fibers are also in part contained in the sympathetic nervous system. Activity varies in different parts of the body. Burn[71] stated that sympathetic vasodilatation is easily demonstrable in the muscles of the dog, detectable in the intestines, and absent in the skin except for that of the ear. He also stated that there are important differences in different species. The rabbit and monkey have no demonstrable sympathetic vasodilators to muscle, the rat has a few, and the dog and the hare many.

Rosenbleuth and Cannon[72] suggested that the vasodilator system consists of autonomic dilators primarily distributed to skeletal muscle, parasympathetic dilators such as the chorda tympani and nervi erigentes, and dorsal root dilators, distributed primarily to the skin and viscera. Sewall and Sanford[73] early recorded the finger volume of patients and found that weak stimulation of the ulnar nerve produced dilatation and stronger stimulation constriction by reflexes activated by stimulation of sensory filaments.

Detailed evidence of the presence or the significance of sympathetic vasodilator fibers to various parts of the body in man cannot be easily obtained. Lewis and Pickering[74] reported evidence for the presence of sympathetic vasodilators to the fingers. This evidence was obtained by heating the body of patients and observing the color response of a cool extremity. Until further study demonstrates the presence and distribution or the absence of sympathetic vasodilators in man a possible relationship to the current surgical treatment of vascular disease must receive consideration.

A sympathectomy in a patient might interrupt vasodilator pathways to such important structures as muscle. It might interrupt the afferent sensory fibers from the viscera that travel in the sympathetic nerves and have been described in dogs by Moore and Singleton.[75] It might also interrupt autonomic proprioceptive fibers from smooth muscle (Langworthy[12]). Interruption of afferent pathways could alter extrasympathetic as well as sympathetic vasodilator reflexes. Splanchnicectomy might also interfere with the vasodilatation of the intestines produced by small doses of adrenalin, as has been reported in acute experiments in the dog and cat by Hartman and Fraser.[76] While lumbar sympathectomy alone in acute experiments did not abolish the vasodilating action of small doses of adrenalin, Wierzuchowski,[77] and Hartman and Fraser[76] did observe that complete denervation, both sympathetic and somatic, abolished this action of adrenalin in perfused hind legs of the dog. Similarly, Wierzuchowski[77] observed that there was no vasodilatation from adrenalin in isolated and perfused hind legs of frogs, or in similarly treated rabbits' ears and heads. There was also no reversal of the action of F 933 under these conditions. It would, therefore, seem that adrenalin vasodilatation would be influenced by sympathectomy more in the splanchnic or visceral area than in extremities.

Postural hypotension is evident in man after extensive sympathectomies. Exercise in extensively or completely sympathectomized patients, dogs, and

cats causes a lowering rather than an elevation of blood pressure. Until more information related to the subject is available, the possibility exists that extensive sympathectomies in man may alter vasodilator mechanisms as well as interrupt vasoconstrictor pathways.

The functional balance between sympathetic vasoconstrictors and sympathetic vasodilators and the functional effect of sympathectomy upon circulation evidently differs from organ to organ and structure to structure. McDowall[7] has reviewed the detailed experiments that indicate that sympathetic vasoconstrictors extend to almost every organ and structure of the body but that vasodilators are preponderantly evident to some. Heymans, Bouckaert, and Regniers[78] have reviewed the complex role played by the modulator nerves of the carotid sinus and the heart and the aorta. These nerves act through the vasomotor centers to control the balance between vasoconstrictors and vasodilators. The old principle that excitement, sham rage, and hemorrhage may contract the vessels of the skin, the spleen, and the splanchnic region and at the same time assure adequate circulation through the vessels of the heart, brain, and muscles is to an important degree dependent upon this balance. Sympathectomy would increase circulation least in those organs that receive a preponderant vasodilator influence.

The Function of Arteriovenous Anastomoses.—Certain organs have a shunt mechanism that further complicates the effect of sympathectomy. These shunts are especially evident in the skin where they aid the regulation of body heat. They conduct blood directly from fine arteries to fine veins, and are called arteriovenous anastomoses. The development of our understanding of the importance of these direct communications has been well reviewed by Clark.[79] Arteriovenous anastomoses are known to exist in man in the penis, fingers, and toes, and probably have a wider distribution as they are known to have in animals. The occurrence of painful glomus tumors in patients demonstrates both their presence and their rich nerve supply.

Anastomoses in the rabbit's ear constrict with adrenalin and faradic stimulation of sympathetic nerves and dilate after histamine and acetylcholine. When widely open they may conduct oxygenated arterial blood directly into veins at the expense of the capillary circulation. Their general behavior is similar to the activity of small arteries and arterioles although irregular periodic contractions are more active and less dependent upon changes of the general circulation. A sympathectomy to an area, should it open widely these shunts, might effect an increase of circulation through these multiple arteriovenous fistulas without increasing the supply of blood to the tissues through the capillaries.

Humoral and Metabolic Control of Circulation Through Denervated Vessels.—Release of central vasomotor tone by sympathectomy does not protect the vascular bed from responding to many humoral influences. Adrenalin may be liberated by the adrenal glands of most patients after regional head, arm, or leg sympathectomies during exercise, nervous strain, and exposure and may have an enhanced reaction upon the denervated vascular bed. Sympathin will

experimentally accelerate a denervated heart (Newton, Zwemer, and Cannon[80]) and elevate blood pressure (Cannon and Bacq[81]). Therefore, if sympathin is clinically significant it may have an action on denervated blood vessels similar to that of adrenalin.

Following an accurate splanchnicectomy the denervated adrenals should not secrete unless or until regeneration occurs. Stewart and Rogoff[82] demonstrated that denervation of the adrenal glands of cats arrested the spontaneous liberation of adrenalin that they believe occurs, and also the liberation affected by nerve stimulation. Sympathin production may also be cut down as sympathetic denervation of patients is extended to the subtotal or total sympathectomy. The more extensive sympathectomies currently employed for hypertension should therefore be less limited by adrenalin-like hormones.

Another humoral agent, angiotonin (Page and Helmer[83]), or hypertensin (Munoz, Braun-Menendez, Fasciolo, and Leloir[84]), may occur in hypertension. It is associated with an alteration of renal circulation and metabolism. This agent may act directly upon blood vessels deprived of their sympathetic nerve supply even after complete experimental sympathectomy (Heymans, Bouckaert, Elaut, Bayless, and Samaan,[85] Freeman and Page,[86] Alpert, Alving, and Grimson,[87] Verney and Vogt[88]). Principles from the pituitary and the adrenal cortex seem to influence the capillaries more than the smaller arteries or arterioles.

Experiments dealing with blood flow and blood vessel dilatation in muscles during rest and activity, experiments dealing with reactive hyperemia, and those dealing with warming and cooling of smooth muscle all indicate that tissue metabolism and metabolic products may influence the peripheral vascular bed. Dale[89] has reviewed the pharmacology of histamine and its action on capillaries and small vessels and that of acetylcholine and its action on arterioles and small arteries, and that of other substances originating peripherally and acting upon the vascular bed. Cannon[8] discussed the possible influence upon blood vessels of lactic acid, carbon dioxide, lack of oxygen, histamine, acetylcholine, and many products of metabolism and concluded: "We have no decisive evidence regarding the agencies which adapt the tone of the blood vessels to the needs of organs as they vary between rest and activity."

Temperature may profoundly influence blood flow and metabolism in sympathectomized limbs (Freeman[90] and Freeman and Zeller[91]). These authors have shown that coldness of the hands or feet of patients with certain vascular disorders may markedly effect local metabolic control of blood vessels. Infection may warm up previously cool extremities and locally improve circulation. The normal skin temperature gradient with the hands and feet usually several degrees cooler than the body must have some metabolic influence upon the blood vessels and might influence the development of certain peripheral vascular diseases.

Further Limitations of Preganglionic Sympathectomy.—Decentralization of the stellate or the lower lumbar sympathetic ganglia for peripheral vascular disease is at present currently popular. There are, however, limitations to this procedure in addition to the increased likelihood of nerve regeneration.

It has been assumed that all synapses between pre- and postganglionic fibers supplying the arm are located in the stellate and second thoracic ganglia, and those supplying the leg in the third and fourth lumbar and sacral ganglia. Preganglionic fibers to the arm travel through the anterior spinal roots from the third, fourth, or fifth thoracic segments to about the ninth. Fibers to the leg travel from the lower one, two, or three thoracic segments to and through the third lumbar. It is possible that as these preganglionic fibers pass through the sympathetic chain toward the upper thoracic or the lower lumbar and sacral ganglia some may form synapses with cells that then send postganglionic fibers to the limbs. Surgical division of the thoracic chain between the second and third dorsal or the lumbar chain just above the third lumbar vertebra would then be a postganglionic sympathectomy for such fibers. Experiments determining the presence or absence of synapses between pre- and postganglionic fibers central to the site of the usual "preganglionic" sympathectomies have not been reported. Evidence of pathways other than those usually recognized has been obtained in patients (Foerster[92]) and in dogs (Derom and Grimson[93]). This evidence indicates that some sympathetic vasoconstrictor fibers entering the midthoracic sympathetic chain may reach the cervical ganglia before returning through the stellate ganglia to the arm. Livingston[94] and Sheehan[11] discussed the possible role of postganglionic cells, located proximal to the operative field of an arm or leg ganglionectomy, in late nerve regeneration. The so-called preganglionic sympathectomies may then be also postganglionic sympathectomies for an undetermined number of sympathetic fibers. The preganglionic sympathectomy is also postganglionic for those postganglionic cell bodies that are destroyed by ischemia or fibroses after transplantation or encapsulation performed to diminish regeneration.

Although isolated or decentralized sympathetic ganglia lose by degeneration the postganglionic fibers passing through them, they remain as a group of relatively intact postganglionic cells. These cell stations would maintain their postganglionic connection with blood vessels and might be capable of influencing vascular tone by automatic activity, or by stimulation by reflex or humoral influences.

Sternschein[95] reviewed the early evidence indicating that a decentralized sympathetic ganglion may exert a tonic influence through its postganglionic fibers. From experiments upon the relationship between the cervical ganglia and the pupil of the rabbit and the cat he concluded that the superior cervical ganglion augments or increases the central dilator tonus that it transmits from the central nervous system and also suppresses dilator tonus of peripheral or humoral origin. Boshamer[96] concluded from experiments in the frog that sympathetic ganglia disconnected from the spinal cord assist the new tone of blood vessels. He suggested that this phenomena might explain the difference between pre- and postganglionic sympathectomies observed by Meltzer and Auer.[39] Hermann and Guiran[97] reviewed and further amplified the experiments with frogs indicating vasoconstrictor tonus originating in sympathetic ganglia. Heymans and Brouha[6] reviewed later evidence for and against the assumption that decentralized sympathetic ganglia might exert a tonic influ-

ence through their postganglionic fibers and concluded that they do effect some control. Emphasis has been placed upon the observations of Govaerts and Bremer[98] that the decentralized superior cervical ganglion of a cat develops a tonic influence upon heart rate after several days and that action currents reappear in the postganglionic cardiac nerves.

Evidence that decentralized ganglia may exert an influence upon blood pressure may also be obtained by comparing the results of experiments employing low cervical cord section, cord destruction, and total sympathectomy in dogs. Physiologists have long recognized that low cervical cord section lowers blood pressure to around 50 to 80 mm. of mercury, but that a recovery toward normal values occurs within twenty-four hours. Also, the cord destruction experiments described previously[64, 65] indicate a similar immediate lowering of pressure and a return to normal within one day or two. In these two types of experiments the sympathetic ganglia and their postganglionic fibers remain intact. The effect upon blood pressure of removal of the ganglia of the paravertebral sympathetic chains, "total sympathectomy," is however somewhat different. I have, in unpublished experiments, combined the two transthoracic and the transabdominal sympathectomies of total sympathectomy in dogs into one operation. Four survived two to seven days. Blood pressures were maintained between 40 and 86 mm. Hg. These values compare favorably with values observed in dogs immediately after cord section or cord destruction. Removal of the paravertebral chains and ganglia for chronic physiologic experiments is usually accomplished by employing three consecutive operations at intervals of several weeks.[30] A lowering of blood pressure occurs only after the second or third operation. Restoration begins within a few weeks of the last operation and reaches the preoperative level in an average time of six months. It is thus evident that while the presence of an intact paravertebral sympathetic chain, with its ganglia and postganglionic connections, facilitates prompt restoration of near normal blood pressure values and of peripheral resistance of the body as a whole, the absence of the paravertebral ganglia delays recovery until sympathetic nerve regeneration may occur.

The exact nature of the influence exerted by decentralized sympathetic ganglia upon the vascular bed has not been demonstrated but may be discussed. Hermann, Morin, and Vial[65] stated that they are inclined to believe that the sympathetic ganglia manage extramedullary vasomotor tone but they stated that their opinion concerning the action of the ganglia is not certain. Origin in sympathetic ganglia of automatic activity has little physiologic basis and is not currently accepted. I believe, however, that the experiments related here may be explained by the assumption that sympathetic ganglia are capable of modifying vascular tone by reflex activation from stimuli that it may receive from the vascular bed. Langworthy[12] has presented evidence that the entire autonomic system, sympathetic and parasympathetic alike, is influenced to an important degree by stimuli received from smooth muscle. He stated: "The autonomic system has been considered as purely a motor system, composed of preganglionic and postganglionic neurons. However, it is influenced by sensory

impulses originating in the smooth muscle and glandular tissues, so that it operates on the basis of segmental reflex arcs. The normal function of smooth muscle is dependent on proprioceptive stimuli from the muscle itself. The autonomic fibers are also subject to control from all levels of the central nervous system, including the motor cortex."

Decentralized sympathetic ganglia may also be stimulated directly by humoral agents. This would influence the tone of the vascular bed supplied by its postganglionic fibers. Cannon and Rosenbleuth[99] have demonstrated that acetylcholine has a much greater effect in stimulating the superior cervical sympathetic ganglion chronically deprived of its preganglionic innervation than the superior cervical ganglion acutely denervated. Burn[100] has reviewed the relation of adrenalin to acetylcholine in the nervous system and the relation of both to the function of sympathetic ganglia.

Abnormal Spasm of the Peripheral Vascular Bed.—Many of the limitations of sympathectomy discussed here have related to the circumstances encountered in relatively normal blood vessels. The occurrence of abnormal local spasm of the vascular bed in Raynaud's disease has interested surgeons since the report of Adson and Brown[55] that sympathectomy afforded relief. Lewis[101] observed the development of skin discoloration associated with local cooling, and the effect of local heating of the hands of patients with Raynaud's disease. He demonstrated that the spasm may occur as a local fault not related to abnormal vasoconstrictor tone. Postganglionic sympathectomy effected by blocking the ulnar nerve with nococain improved discoloration already present only partially and partially retarded the subsequent development of local blood vessel spasm. Occurrence of some degree of spasm in patients after pre- or postganglionic sympathetic denervation is a common observation. Sympathectomy in this form of vasospastic disease is then limited both by mechanisms controlling the normal vascular bed and by a superimposed local abnormality of the blood vessels.

CLINICAL INTERPRETATION

Partial or complete excision or decentralization of the ganglionated paravertebral sympathetic chain may effect varying degrees of relaxation of the smooth muscle of blood vessels and some increase of circulation. It does not effect complete relaxation of blood vessels or great increase of blood flow. The vasomotor fibers of the sympathetic nervous system are largely the efferent pathways of a complex proprioceptive mechanism that regulates or modulates the peripheral resistance but is not responsible for its maintenance. The therapeutic effect of interruption of these efferent sympathetic pathways for disease is limited by the factors just reviewed that are responsible for the maintenance in denervated blood vessels of tone and control. The most important of these factors is the inherent ability of smooth muscle to maintain an independent tone. Another important factor is the ability of these muscles to respond to humoral substances such as adrenalin, acetylcholine, and angiotonin, or hypertensin, to products of tissue metabolism such as lactic acid,

carbon dioxide, and histamine, and to changes of temperature. Blood vessels may be to some extent under extra sympathetic nervous control or, if the denervation be preganglionic, under reflex or other restraining control through the isolated ganglia. Late after sympathectomy, preganglionic nerve regeneration through isolated ganglia or postganglionic nerve regeneration from cells central to the operative defect may occur.

Regardless of these and the other limiting factors that have been reviewed, temporary or permanent interruption of the sympathetic pathways accomplishes certain therapeutic benefits for patients with many disease processes. The greatest benefits are achieved in disease processes associated with a disturbance of the proprioceptive regulatory function of the sympathetic nervous system. An example of the encouraging results that may be obtained in patients with a central disturbance of the reflex proprioceptive mechanism is afforded by the effectiveness of sympathectomy in patients with a neurogenic variety of hypertension.[102] An example of the results in patients with a peripheral disturbance of the reflex proprioceptive regulation is afforded by the effectiveness of sympathetic block in relieving the spasm of collateral vessels that develops after extensive vascular injury or arterial embolism. There are, however, not many disease processes that can originate as abnormal central or reflex sympathetic vasoconstriction.

Sympathectomy may also benefit patients with conditions such as Raynaud's disease, scleroderma, thromboangiitis obliterans, and arteriosclerotic vascular occlusion that evidently are not initiated by excess sympathetic tone. Benefits in patients with these conditions may be largely related to increase of the temperature of the extremity, to a slight improvement of circulation, and to elimination by the sympathectomy of the constant fluctuations of tone that are ordinarily induced by the vasomotor nerves. It is common observation that treatment of peripheral vascular diseases by sympathectomy is more satisfactory in the legs than in the arms. There seems to be evidence that the legs, because of their dependent position, are more actively influenced by sympathetic vasomotor tone of proprioceptive origin. Sympathectomy may then effect its greater benefit to the legs by interrupting this tone and also by introducing, during changes of posture, an uncompensated passive vascular exercise.

Surgeons have not agreed upon the form of sympathectomy that should be employed for peripheral vascular disease of the extremities. It seems to me that the sympathectomy should be a radical ganglionectomy to minimize nerve regeneration and to eliminate any buffering or reflex control that might be afforded by decentralized ganglia. It also seems that the "adrenalin sensitization" phenomenon, upon which the preganglionic type of sympathectomy is based, is not sufficiently important clinically to warrant risking regeneration. Both a ganglionectomy and a preganglionic sympathectomy "sensitize" blood vessels to adrenalin. I employ preganglionic sympathectomy only in instances of disease of one arm since a unilateral Horner's syndrome may be objectionable.

Special problems have become important clinically as sympathectomy has been extended for the treatment of hypertension to include part or all of the trunk and the viscera as well as the extremities. These have been reviewed.

It seems important that there are sympathetic vasodilator pathways to muscle and to many of the viscera. Circulation through organs preponderantly supplied by vasodilators will not be improved as much as it will in those preponderantly supplied by vasoconstrictors. Clinical studies have demonstrated that although the circulation of an extremity alone may be increased by regional sympathectomy, the over-all circulation of the entire body after subtotal to total sympathectomy is, as evidenced by the cardiac output, somewhat decreased.

Clinical experience with the treatment of hypertension seems to indicate that elimination of abnormal reflex vasoconstrictor tone of central origin more effectively reduces blood pressure as sympathectomy of the body is made more and more complete. The splanchnic area, including the kidneys and the adrenal glands, does not seem to be more important than other large vascular areas of the body.[30, 103] Extensive sympathectomy also interferes with normal reflex adjustments of vasoconstrictor tone that occur with changes of position of the body. Difficulties with postural hypotension seem to be greater when denervation is directed toward the dependent half of the body, as it is in the techniques used for splanchnicectomy, than when it is directed toward the upper three-quarters or all of the body as it is with the subtotal to total paravertebral sympathectomy.

The physiologic and anatomic changes effected by regional or extensive sympathectomy are complex. Experimental investigation has contributed valuable information but has not solved all of the problems. The surgeon still has difficulty determining the indications for and the results of various procedures. The value of the novocain block as a prognostic procedure is questionable since it effects an acute change of circulation and does not represent the conditions that will maintain several days, months, or years, after a sympathectomy. It does not indicate the long-term influence upon a chronic peripheral vascular disease process that may result from elimination by sympathectomy of central proprioceptive influences. Similarly evaluation of the late result of a sympathectomy may be difficult and easily misjudged because of enthusiasm. Fortunately, sympathectomy is a relatively safe surgical procedure if detailed general examination of the patient demonstrates no contraindication. It remains a valuable adjunct to the conservative treatment of peripheral vascular disease.

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Book Reviews

Neuro-Ophthalmology. By Donald J. Lyle, B.S., M.D., Department of Anatomy, Medical College, University of Cincinnati, Cincinnati, Ohio. Ed. 1. Pp. 395, with 234 illustrations. Springfield, Ill., 1945, Charles C Thomas, Publisher. $10.50.

This book according to the preface is written to bring together, in brief but comprehensive and coordinated manner, those many phases of neurology, in so far as they concern, directly or indirectly, neuro-ophthalmology.

The result is another textbook of neurology with special reference to ophthalmology. It is tedious reading, perhaps due to its brevity. As a reference book it should be very useful to the ophthalmologist who is untrained in neurology.

The following paragraph, p. 81, gives one the impression that the author is writing about a subject with which he has not had a wide experience.

"The ophthalmic division is most frequently involved in trigeminal neuralgia. The supra-orbital branch is particularly affected. ---------- The ophthalmic or first division is less frequently involved by tic douloureux than either the second or third. The third is most commonly affected."

An extensive bibliography of 1718 references grouped alphabetically is listed at the end of the book, some of which are referred to by numbers in the text, but many are not.

The 234 illustrations are all well reproduced.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

TEXTBOOK OF ANESTHETICS. By R. J. Minnitt, M.D., D.A., and John Gillies, M.C., M.B., Ch.B., D.A., Royal Infirmary, Edinburgh, Scotland. Cloth. Price $7. Pp. 487, with 199 illustrations. Baltimore, 1944, Williams & Wilkins Company.

PYE'S SURGICAL HANDICRAFT. Edited by Hamilton Bailey, F.R.C.S., England. Cloth. Price $8. Pp. 628, with 724 illustrations. Baltimore, 1944, Williams & Wilkins Company.

POET PHYSICIANS (An Anthology of Medical Poetry Written by Physicians). Compiled by Mary Lou McDonough. Cloth. Price $5. Pp. 204. Springfield, Ill., 1945, Charles C Thomas, Publisher.

PERIPHERAL NERVE INJURIES: PRINCIPLES OF DIAGNOSIS. By Captain Webb Haymaker, M.C., A.U.S., Army Institute of Pathology, Washington, D. C., and Major Barnes Woodhall, M.C., A.U.S., Chief Neurology Section, Walter Reed Hospital, Washington, D. C. Cloth. Pp. 227, with 225 illustrations. Philadelphia and London, 1945, W. B. Saunders Company.

MODERN METHODS OF AMPUTATION. By Edmundo Yasconcelos, Professor, University of Sao Paulo. Introductory Survey by Major General Norman T. Kirk. Cloth. Price $10. Pp. 253, with 258 illustrations. New York, 1945, Philosophical Library, Inc.

DUODENAL AND JEJUNAL PEPTIC ULCER. By Rudolf Nissen, M.D., Attending Surgeon, Jewish Hospital of Brooklyn. Cloth. Pp. 143. New York, 1945, Grune & Stratton, Inc.

RADIOLOGIC EXAMINATION OF THE SMALL INTESTINE. By Russ Golden, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University. Cloth. Price $6. Pp. 239, with 75 illustrations. Philadelphia, 1945, J. B. Lippincott Company.

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. By Maurice Feldman, M.D., Assistant Professor, Gastroenterology, University of Maryland. Cloth. Price $7. Pp. 769. Baltimore, 1945, Williams & Wilkins Company.

PENICILLIN THERAPY INCLUDING TYROTHRICIN AND OTHER ANTIBIOTIC THERAPY. By John A. Kolmer, M.S., M.D., Dr. Ph., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and School of Dentistry, Temple University. Cloth. Pp. 302. New York, 1945, D. Appleton-Century Company, Inc.

NEURO-OPHTHALMOLOGY. By Donald J. Lyle, B.S., M.D., Department of Anatomy, Medical College of the University of Cincinnati. Cloth. Price $10.50. Pp. 395, with 234 illustrations. Springfield, Ill., 1945, Charles C Thomas, Publisher.

DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE. By Frank R. Ford, M.D., Associate Professor of Neurology, The Johns Hopkins University. Cloth. Pp. 1,143, with 164 illustrations. Springfield, Ill., 1944, Charles C Thomas, Publisher.

ESSENTIALS OF BODY MECHANICS IN HEALTH AND DISEASE. By J. T. Goldthwait, M.D., F.A.C.S., LL.D., L. T. Brown, M.D., F.A.C.S., L. T. Swaim, M.D., John G. Kuhns, M.D., F.A.C.S., and Wm. J. Kerr, M.D., F.A.C.P. Cloth. Price $5. Pp. 337, with 128 illustrations. Philadelphia, 1945, J. B. Lippincott Company.

MODERN MEDICINE ANNUAL 1944. Abstracted Articles of Various Authors. Cloth. Pp. 853. Minneapolis, 1945, Modern Medicine Publishing Company.

CLINICAL TRAUMATIC SURGERY. By John J. Moorhead, B.S., M.D., D.Sc., F.A.C.S. (D.S.M.), Columbia University. Cloth. Pp. 747, with 500 illustrations. Philadelphia, 1945, W. B. Saunders Company.

A MANUAL OF SURGICAL ANATOMY. By Tom Jones and W. C. Shepard, Office of the Surgeon General, National Research Council, Washington, D. C. Cloth. Pp. 195, with 139 illustrations. Philadelphia, 1945, W. B. Saunders Company.

BONE GRAFTING IN THE TREATMENT OF FRACTURES. By J. R. Armstrong, M.D., M.Ch., F.R.C.S., Orthopaedic Department with Fracture Clinic, Charing Cross Hospital, London. Cloth. Price $7. Pp. 175, with 204 illustrations. Baltimore, 1945, Williams & Wilkins Company.

RYPIN'S MEDICAL LICENSURE EXAMINATIONS. By Harold Rypins, M.D., Edited by Walter L. Bierring, M.D., National Board of Medical Examiners. Cloth. Price $6. Pp. 545. Philadelphia, 1945, J. B. Lippincott Company.

THE YEAR BOOK OF GENERAL SURGERY 1944. Edited by Evarts A. Graham, A.B., M.D., Washington University School of Medicine, St. Louis, Mo. Cloth. Price $3.00. Pp. 736, with 271 illustrations. Chicago, 1944, The Year Book Publishers, Inc.

THE URINARY TRACT, A HANDBOOK OF ROENTGEN DIAGNOSIS. By H. Dabney Kerr, M.D., and Carl L. Gillies, M.D., Iowa City. Cloth. Price $5.50. Pp. 320, with 475 illustrations. Chicago, 1944, The Year Book Publishers, Inc.

FRACTURES OF THE JAWS. By Robert H. Ivy, M.D., D.D.S., F.A.C.S., and Lawrence Curtis, A.B., M.D., D.D.S., F.A.C S., University of Pennsylvania. Cloth. Price $4.50. Pp. 174, with 199 illustrations. Philadelphia, 1945, Lea & Febiger.

NITROUS OXIDE-OXYGEN ANESTHESIA. By Major F. W. Clement, M.D., M.C., A M.S. Cloth. Price $4.50. Pp. 288, with 92 illustrations. Philadelphia, 1945, Lea & Febiger.

THE INTERVERTEBRAL DISC. By F. Keith Bradford, M.D., Houston, and R. Glen Spurling, M.D., Louisville. Cloth. Price $4.00. Pp. 192, with 70 illustrations. Springfield, Ill., 1945, Charles C Thomas, Publisher.

PEDIATRICS X-RAY DIAGNOSIS. By John Caffey, A.B., M.D., New York. Cloth. Price $12.50. Pp. 838, with 711 illustrations. Chicago, 1945, The Year Book Publishers, Inc.

A TEXTBOOK OF SURGERY. By John Homans, M.D., Clinical Professor of Surgery, Emeritus. Cloth. Price $8.00. Pp. 1,278, with 530 illustrations. Springfield, Ill., 1945. Charles C Thomas, Publisher.

TEXTBOOK OF OBSTETRICS. By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College. Cloth. Pp. 1,277, with 740 illustrations. New York, 1945, D. Appleton-Century Company, Inc.

A TEXTBOOK OF NEURO-ANATOMY. By Albert Kuntz, Ph.D., M.D., Professor of Micro-Anatomy, St. Louis University School of Medicine. Cloth. Price $6.50. Pp. 478, with 328 illustrations. Philadelphia, 1945, Lea & Febiger.

A HANDBOOK OF ROENTGEN DIAGNOSIS, THE OSSEOUS SYSTEM. By Vincent W. Archer, M.D., Professor of Roentgenology, University of Virginia Department of Medicine. Cloth. Price $5.50. Pp. 320, with 148 illustrations. Chicago, 1945, The Year Book Publishers, Inc.

CLASSIC DESCRIPTIONS OF DISEASE. By Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine. Cloth. Price $6.50. Pp. 679, with 158 illustrations. Springfield, Ill., 1945, Charles C Thomas, Publisher.

HEY GROVES' SYNOPSIS OF SURGERY. Edited by Cecil P. G. Wakely, C.B., D.Sc., Senior Surgeon, King's College Hospital. Cloth. Price $6.00. Pp. 632, with 195 illustrations. Baltimore, 1945, Williams & Wilkins Company.

A HANDBOOK FOR DISSECTORS. By J. C. Boileau Grant, M.D., Professor of Anatomy, University of Toronto, and H. A. Cates, Associate Professor of Anatomy, University of Toronto. Cloth. Price $3.50. Pp. 390, with 10 illustrations. Baltimore, 1945, Williams & Wilkins Company.

FRACTURES AND ORTHOPAEDIC SURGERY FOR NURSES AND MASSEUSES. By Arthur Naylor, Ch.M., M.D., Res. Surg. Officer, Westwood E.M.S. Hospital. Cloth. Price $5.00. Pp. 288, with 243 illustrations. Baltimore, 1945, Williams & Wilkins Company.

ACUTE INJURIES OF THE HEAD, THEIR DIAGNOSIS, TREATMENT COMPLICATIONS AND SEQUELS. By G. F. Rowbotham, B.Sc., Surgeon in Charge, Department of Neurological Surgery, Newcastle General Hospital. Cloth. Price $8.50. Pp. 424, with 201 illustrations. Baltimore, 1945, Williams & Wilkins Company.

VARICOSE VEINS OF THE LOWER EXTREMITIES (Monograph). By Anthony M. Barone, M.D., 4000 West North Avenue, Chicago, Ill. Paper. Pp. 51, with 10 illustrations.

PHYSICAL CHEMISTRY OF CELLS AND TISSUES. By Rudolf Höber, M.D., Department of Physiology, University of Pennsylvania. Cloth. Price $9.00. Pp. 676, with 70 illustrations. Philadelphia, 1945, The Blakiston Company.

GENERAL AND PLASTIC SURGERY. By J. Eastman Sheehan, M.D., Professor of Plastic Reparative Surgery, New York Polyclinic Medical School and Hospital. Cloth. Price $6.75. Pp. 345, with 495 illustrations. New York, 1945, Paul B. Hoeber, Inc.

THE MARCH OF MEDICINE. By the New York Academy of Medicine, Lectures to the Laity, composed of Charles D. Ryan, M.D., Frank Fremont Smith, M.D., Philip Potter, M.D., Alexander T. Martin, M.D., George F. Cahill, M.D., George T. Ward, M.D., and Wilson G. Smillie, M.D. Cloth. Price $1.75. Pp. 121. New York, 1945, Columbia University Press.

AMPUTATION PROSTHESIS. By Atha Thomas, M.D., F.A.C.S., Associate Professor of Surgery (Orthopedics), University of Colorado School of Medicine, and Chester C. Haddan, President of the Association of Limb Manufacturers of America. Cloth. Price $8.00. Pp. 305, with 207 illustrations. Philadelphia, 1945, J. B. Lippincott Company.

MODERN UROLOGY FOR NURSES. By Sheila Maureen Dwyer, R.N., B.S., Director of Nursing, Southampton Hospital, Southampton, New York, and George W. Fish, M.D., Associate Professor of Urology, College of Physicians and Surgeons, Columbia University, New York. Cloth. Price $3.25. Pp. 287, with 66 illustrations. Philadelphia, 1945, Lea & Febiger.

PATHOLOGY IN SURGERY. By N. Chandler Foot, M.D., Professor of Surgical Pathology, Cornell University Medical College, Surgical Pathologist, New York Hospital. Cloth. Pp. 489, with 368 illustrations. Philadelphia, 1945, J. B. Lippincott Company.

Announcement

Urology Award

The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deems none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Netherland Plaza, Cincinnati, Ohio, July 22 to 25, 1946.

Essays must be in the hands of the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tenn., on or before July 1, 1946.